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ANTAGONISM OF THERAPEUTIC AGENTS:

AND WHAT IT TEACHES.

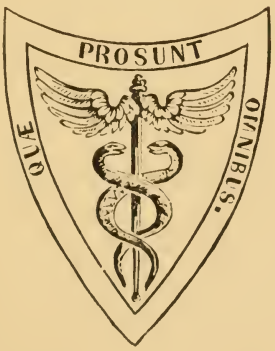
THE ESSAY TO WHICH WAS AWARDED THE FOTHERGILLIAN GOLD MEDAL OF THE MEDICAL SOCIETY OF LONDON FOR 1878.

BY

J. MILNER FOTHERGILL, M.D., EDIN.,

MEMBER OF THE ROYAL COLLEGE OF PHYSICIANS OF LONDON,
ASSISTANT PHYSICIAN TO THE WEST LONDON HOSPITAL,
AND TO THE CITY OF LONDON HOSPITAL FOR DISEASES OF THE CHEST,
VICTORIA PARK.

"In judging of the value of a therapeutical method the one and only criterion is success."—BURDON SANDERSON.



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TO

T. LAUDER BRUNTON, M.D., Sc.D., F.R.S.,

A LEADER

OF PHYSIOLOGICAL INQUIRY INTO

THE ACTION OF THERAPEUTIC AGENTS, IN GREAT BRITAIN,

THIS LITTLE WORK IS AFFECTIONATELY

Dedicated

BY

THE AUTHOR.

PREFACE.

THE aim of the writer, in this Essay, is to present a fair bird's-eye view of the subject of the antagonism of toxic agents, so far as this is possible at the present time. First, the experimental part of the subject is given; and then the practical bearing of these experimental researches. There is no unnecessary writing, as the subject is given as briefly as it will permit. Experiments which led to nothing are omitted, and those which gave positive results are not given at full length, but just the main results attained; and an illustrative experiment or two are alone related in detail. The practical bearings of the different experiments have been kept prominently in view throughout.

23 SOMERSET STREET,
PORTMAN SQUARE, W.
June 1, 1878.

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THE ANTAGONISM

OF

THERAPEUTIC AGENTS:

AND WHAT IT TEACHES.

CHAPTER I.

EXPERIMENTAL INQUIRY.

This highly interesting subject has only very recently come prominently before the medical profession. The youngest born of the therapeutic family, it already, however, promises to be one of the most active and vigorous of the various groups. Only a very few years ago all that we knew almost was confined to chemical antidotes. Alkalies would neutralize acids in the stomach; tannin would form an insoluble compound with tartar emetic, albumen with corrosive sublimate; sulphuric acid would form an inert compound with lead; and the hydrated sesquioxide of iron would precipitate arsenious acid—provided of course that it was at hand in sufficient quantity. But these actions were confined to the poison still remaining in the alimentary canal; and nothing could be done as to that

which was absorbed, but to wait and see whether the organism could eliminate it successfully, or perish in a vain attempt. Perhaps this statement needs some qualification as regards sulphuric acid and lead compounds, but broadly it is quite true. Chemical antidotes formed the frontier to which medical knowledge had advanced up to a very recent date—except some vague knowledge as to the antagonism existing betwixt opium and belladonna.

The first dawnings of what promises to be the most potent and withal most precise subject connected with therapeutics, commencing, as have many other important measures, outside the profession—the first use of one drug to modify and counteract another—was that of the use of opiates to relieve the symptoms produced by an overdose of belladonna. It appears that belladonna used to be given to relieve thirst by Italian pedlers in the sixteenth century (1570), and occasionally an overdose was given, and then opiates were resorted to in order to modify the effects. Such was the beginning of any knowledge of the antagonism of remedies, a matter now being systematically studied with the greatest attention.

The first definite attempt to utilize this antagonism of opium and belladonna occurred in 1661, when Horstius gave opium to relieve the consequences of a large dose of belladonna. From that time forward one drug has been used to overcome the effects of an overdose

of the other. Hyoscyamus and stramonium, as well as belladonna, were given in opium-poisoning with indecisive results. Professor Frazer, F.R.S., thinks the experiments of Bois, Camus, Onsum, and Brown-Séquard insufficient to show that the lethal effects of opium can be warded off by these agents, but holds that they do demonstrate that there are contrary or antagonistic actions of these agents which may be utilized. We shall see further on, that one of these contrary or antagonistic actions, namely, the effect upon the skin, may be utilized in practice with the happiest effects.

This form of experimentation as to the antagonistic effect of various drugs has been chiefly conducted in England, though arising first abroad. One of the first investigations was that of Professor Preyer, of Jena, who published in 1870 the results of experimentation as to the antagonism of atropia and prussic acid. He showed that the lethal action of prussic acid was due to embarrassment of the lungs and heart by its action on the terminal branches of the vagi in these organs, and thought that the action of belladonna was antagonistic and opposed to this; but the experiments were not carried out completely, and were not corroborated by a series of experiments on the same subject instituted by Bartholow, of Cincinnati. The action of another agent, muscarine, upon the action of atropia was studied experimentally by Schmiedeberg and Koppe,

who published a memoir on this subject in 1869. A more or less general antagonism was found.

The effects of belladonna upon the pupil of the eye are so pronounced that they offer a distinct temptation to observers to experiment as to the other actions of drugs which contract the pupil, when given along with it. Thus we have a large and valuable series of observations as to the antagonism which exists betwixt Calabar bean and belladonna. These drugs have an opposite effect upon the iris, and experiments have led to the discovery that they have an antagonistic action in other directions quite as marked. In 1864 Kleinwächter employed the Calabar bean in a case of poisoning by belladonna with distinct relief of the symptoms. Subsequently Bourneville, while trying the effect of physostigma upon tetanus, gave a large and, to the best of his knowledge, a lethal dose of Calabar bean to an animal, and then afterwards, when the symptoms of poisoning were marked, a small quantity of atropine subcutaneously, with the effect that the animal recovered perfectly. Dr. Bartholow made a few not very conclusive experiments as to the antagonism of these two agents in 1870; but it is to the experiments of Professor Frazer that we have to look for the most complete account of this antagonism. The following notes are taken from his famous monograph on the antagonism between the actions of physostigma and atropia. First the minimum fatal dose of atropia

had to be found, and it was ascertained that it was nearly 22 grains for a rabbit weighing 3 lb. Then the minimum fatal dose of extract of Calabar bean was ascertained; and it was found to be 0.4 of a grain per pound, or 1.2 grains for a 3 lb. rabbit. Of sulphate of physostigma the dose was one-tenth ($\frac{1}{10}$) of this, or 0.04 of a grain for every pound.

The first experiments were made with atropia administered before physostigma. To a rabbit weighing 2 lb. 15½ oz., three-tenths ($\frac{3}{10}$) of a grain of sulphate of atropia was administered subcutaneously, and after an interval of five minutes one and a fifth ($1\frac{1}{5}$) grains of extract of physostigma. The rabbit recovered perfectly, though symptoms of poisoning were actively manifested. Ten days afterwards, the rabbit being perfectly well and having in the interval gained in weight, one and a fifth ($1\frac{1}{5}$) grains of extract of physostigma were injected without any atropia. The animal began to manifest symptoms of poisoning in six minutes, and in twenty-two minutes from the time of the injection was dead.

In another instance, to a rabbit weighing 3 lb. 4 oz. the seventeen-hundredth ($\frac{17}{1000}$) of a grain of sulphate of atropia was administered subcutaneously, and five minutes afterwards 3 grains and $\frac{9}{10}$ths of a grain ($3\frac{9}{10}$ gr.) of extract of physostigma were injected. The animal was very ill. In forty minutes the respirations had fallen to 13 times in 10 seconds. After the lapse

of two hours an improvement set in, but it was not till six hours and a half had elapsed from the injection of the physostigma that the paralytic symptoms passed away. It recovered completely. Eight days afterwards, the rabbit having gained an ounce in weight, one grain and three-tenths ($1\frac{3}{10}$)—one-third of the first dose—were administered, and in thirty-one minutes the animal was dead.

In a third case, to a rabbit weighing 3 lb., half ($\frac{1}{2}$) a grain of sulphate of atropia was injected, and in five minutes six-twenty-fifths ($\frac{6}{25}$) of a grain of the sulphate of physostigma were injected (equal to $\frac{60}{25} = 2\frac{10}{25}$ of a grain of extract). The animal was very ill, but recovered, and next day was active and well. Nine days afterwards, the animal being well, and having gained half-an-ounce in weight, the same quantity of sulphate of physostigma was given alone. In eight minutes the respirations consisted of mere gasps; and in nine minutes and fifty seconds the animal was dead.

Then the atropia and physostigma were administered together simultaneously. A rabbit weighing 3 lb. 12 oz. had half ($\frac{1}{2}$) a grain of sulphate of atropia and three (3) grains of extract of physostigma injected simultaneously. This rabbit became very ill, the symptoms of Calabar bean poisoning became very marked, but next day it was about and well. On the tenth day after the experiment $1\frac{1}{2}$ grains of physos-

tigma (half the first dose) were injected; the animal died fifty-four minutes after.

To a fourth rabbit weighing 2½ lb. half (½) a grain of sulphate of atropia and one (1) grain of extract of physostigma were simultaneously administered subcutaneously; severe symptoms followed, but perfect recovery took place. Thirteen days afterwards one (1) grain of extract of physostigma was given alone, and death resulted in eighteen minutes.

Then some experiments were made with the physostigma administered before the atropia.

To a rabbit weighing 3 lb. 2 oz. two and a half (2½) grains of extract of physostigma were administered, and five mintes afterwards half (½) a grain of sulphate of atropia. Though severely ill, it perfectly recovered. Eleven days afterwards the same quantity of the Calabar bean extract was injected, and in eleven minutes and a half the animal died.

To another rabbit, weighing 3 lb. 11½ oz. two (2) grains of physostigma extract were injected, and eight and a half minutes after half (½) a grain of sulphate of atropia. Paralytic symptoms followed, but in one hour and forty minutes every symptom almost had disappeared. Four days afterwards one grain and a half (1½) of the extract of physostigma was injected alone, and in fifteen and a half minutes the rabbit was dead.

Into a rabbit weighing 2 lb. and 14 oz. one and a half (1½) grains of extract of physostigma were injected,

and ten minutes and thirty seconds afterwards, when the animal was flaccid and paralyzed, one and a half ($1\frac{1}{2}$) grains of sulphate of atropia were administered. Eight minutes after this the animal succeeded in rising, sat in a natural position, and quite recovered. Twelve days afterwards the physostigma was given alone, and the animal was dead in thirty minutes.

Similar experiments to the above furnished like results. After giving details of some further experiments Professor Frazer says:—"In these various experiments the influence exerted by atropia upon the action of physostigma is shown to be a most remarkable and conspicuous one, for it effectually counteracts the lethal activity of certain doses of physostigma, whether it be given within a certain time before, simultaneously with, or within a certain time after, that substance."

Some experiments were then made upon dogs in order to test the above results. An experiment was made by injecting three-fifths ($\frac{3}{5}$) of a grain of sulphate of physostigma into a dog weighing 10 lb. 3 oz. and five minutes afterwards (when the animal was already ill) three-tenths ($\frac{3}{10}$) of a grain of sulphate of atropia. In an hour and fifty-five minutes the dog had perfectly recovered, having been very ill. Nineteen days afterwards half the quantity of physostigma, three-tenths ($\frac{3}{10}$) of a grain, was given alone, and in twenty minutes the dog was dead.

Then two (2) grains of extract of physostigma

were injected into the facial vein of a rabbit weighing 4 lb. Five minutes afterwards a thirtieth ($\frac{1}{30}$) of a grain of sulphate of atropia was injected into the same vein. The animal became very ill, and it was not till three hours and ten minutes that it recovered itself completely. Seven days afterwards one grain and seven-tenths ($1\frac{7}{10}$) of the sulphate of physostigma were given alone. In twenty-three minutes the rabbit was dead. Corroborative experiments were performed with like results.

Experiments were then performed to find out how much more than the minimum lethal dose of Calabar bean could be successfully antagonized by atropine. It was found that three and a half ($3\frac{1}{2}$) times the dose could be successfully met by atropine; but not four (4) times the minimum lethal dose. Professor Frazer, too, ascertained, what has been also found by other experimenters, that death could be produced by the combined administration of non-lethal doses of each agent. Thus half the minimum lethal dose of physostigma (·06 of a grain) with nearly half the lethal dose of atropine (10 grs.) (lethal dose 22 grains for a 3 lb. rabbit) given together produce a fatal result. Some further experiments were conducted as to the length of time which might be permitted to elapse betwixt the administration of varying doses of the two agents, which, though of high interest, can scarcely be quoted here.

The whole series of these exact and careful experiments shows how potent atropine is in counteracting the lethal effects of physostigma. Though no particular direct advantage as yet has been found to accrue from these experiments they have been productive of useful practical results, by illustrating the action of Calabar bean, which results will be given in an after section of this essay—the practical section.

The next experiments to be referred to are those of the Edinburgh Committee of the British Medical Association, conducted by the late Professor J. Hughes Bennett. He first ascertained the minimum fatal dose of strychnia in the rabbit, and found it was one ninety-sixth ($\frac{1}{96}$) of a grain for a 3 lb. rabbit, or one two-hundred-and-eighty-eighth ($\frac{1}{288}$) of a grain per pound. The minimum lethal dose of chloral hydrate he ascertained to be seven (7) grains to the pound, twenty-one (21) grains for a 3 lb. rabbit. Experiments were then made with varying quantities of these substances given together with striking results. As it is impossible to give the results of every single experiment, a selection must be made which will show, as fairly as is possible by such selection, the results obtained.

To a rabbit weighing 2 lb. 13 oz. fourteen (14) grains of chloral hydrate were given along with one-seventieth ($\frac{1}{70}$) of a grain of strychnia: the animal recovered. Seven days afterwards the same dose of strychnia alone proved fatal in eighteen minutes.

To a rabbit weighing 3 lb. 3 oz. eight (8) grains of chloral and one-eightieth ($\frac{1}{80}$) of a grain of strychnia were given simultaneously. It recovered, and in seven days died of the same amount of strychnia given alone in twenty (20) minutes.

To a third rabbit weighing 2 lb. 12 oz. eighteen (18) grains of chloral hydrate and one-fortieth ($\frac{1}{40}$) of a grain of strychnia were given together, and the animal recovered. Seven days afterwards the same dose of strychnia proved fatal in twelve (12) minutes.

The antagonism of the two agents is well displayed by these experiments. Even when the animal was in a sound sleep any irritation produced severe twitchings, showing that the reflex excitability of the cord was increased by the strychnia in spite of the chloral sleep.

Then it was determined to ascertain the potency of hydrate of chloral over strychnia-poisoning when given at varying intervals after. To rabbits weighing 3 lb., or within an ounce of that weight, sixteen (16) grains of chloral were administered, and some minutes after, one-ninety-sixth ($\frac{1}{96}$) of a grain of strychnia. Up to eight (8) minutes after the chloral was effective; but if ten (10) or more minutes had elapsed, the chloral was powerless to avert death. Thus, when the chloral was given ten minutes after the strychnia the animal survived over thirty-five (35) minutes; but when given twenty-two minutes after it only survived twenty (20)

minutes. (The first survived forty-five (45) minutes after the administration of the strychnia; the second but forty-two (42) minutes.)

Following out the observations of Oscar Liebreich, that minute doses of strychnia would rouse rabbits out of the coma-sleep of chloral, some experiments to test this effect were made. Here there is a little difficulty to encounter, in that sometimes the chloral killed the rabbit and sometimes the strychnia. Thus to a rabbit weighing 3 lb., twenty-four (24) grains of chloral were given, and fifteen minutes after one-fortieth ($\frac{1}{40}$) of a grain of strychnia; the animal died with spasms and opisthotonos.

To another weighing 3 lb., twenty-three (23) grains of chloral were given, and thirteen minutes afterwards one one-hundred-and-tenth ($\frac{1}{110}$) of a grain of strychnia; the animal died in profound coma.

But in a number of cases results identical with the following were arrived at: To a rabbit weighing 3 lbs 2 oz., twenty-one and a half ($21\frac{1}{2}$) grains of chloral hydrate were given with one-hundredth ($\frac{1}{100}$) of a grain of strychnia, fifteen (15) minutes afterwards the animal recovered, and four days afterwards died of the same dose of chloral alone.

These experiments showed that the injection of strychnia after a fatal dose of chloral exercised but uncertain results; and the animals died comatose even

when twitchings indicated the excited condition of the spinal cord.

Then rats were experimented upon. It was found that with them comparatively smaller doses of chloral and larger doses of strychnia were required. Thus one and seven-eighths ($1\frac{7}{8}$) of a grain of chloral was enough to kill a rat weighing twelve (12) ounces; while one-sixtieth ($\frac{1}{60}$) of a grain of strychnia was the minimum lethal dose. Thus rats die from two grains of chloral to the lb. weight; rabbits seven grains per pound. Rats require one-sixtieth ($\frac{1}{60}$) of a grain of strychnia per pound; rabbits about a three-hundredth ($\frac{1}{300}$), a 3 lb. rabbit taking one-hundredth ($\frac{1}{100}$) for a fatal dose. In order to show the antagonism in rats a case may be quoted where to a rat weighing 11 oz. three (3) grains of chloral were given with one-forty-fourth ($\frac{1}{44}$) of a grain of strychnia. The animal recovered after considerable twitchings. Some time afterwards the animal died of the same dose of strychnia in eighteen minutes. But in this series of experiments occasionally the chloral killed, and at other times the strychnia; still broad results tended to demonstrate the antagonism of these two agents.

Prof. Bennett showed the antagonism of these two agents on several public occasions. He writes: "Take two rabbits of about 3 lb. weight; inject under the skin of both one ninety-sixth ($\frac{1}{96}$) of a grain of strych-

nia and then in one a solution of fifteen (15) grains of chloral; in ten minutes the one will leap into the air and fall down tetanic and dead; the other will go to sleep and in about two hours will wake up as if nothing were the matter. A more certain antidote does not exist."

Experiments were next performed in order to ascertain the antagonism existing betwixt sulphate of atropia and Calabar bean. This matter has been thoroughly investigated by Prof. Frazer, and need not be gone into again. It may be well, however, just to quote what Prof. Bennett says as to the results generally; "An analysis of these cases shows that sulphate of atropia prolongs life, and may even save it, after a fatal dose of Calabar bean. The antagonistic influence of sulphate of atropia on the effects of extract of Calabar bean is not nearly so well marked as that of chloral hydrate as an antagonist to the effects of strychnia." It will be seen further on, that these conclusions of Prof. Bennett's as to the antagonism of hydrate of chloral and strychnia corroborate and confirm the conclusions of Oscar Liebreich, of Berlin, also arrived at by experimentation.

To follow Prof. Bennett, the next investigation was to test for the effects of hydrate of chloral and Calabar bean given together.

Thus, to a rabbit weighing 3 lb. 12 oz. fifteen (15) grains of hydrate of chloral were given, and fourteen

minutes afterwards a quarter ($\frac{1}{4}$) of a grain of extract of Calabar bean, with the result of recovery. The experiment was varied as to dose and time with somewhat different results, so it was determined to try a crucial test.

Thus, for instance, fifteen (15) grains of chloral were given to a rabbit weighing 3 lb., and fifteen minutes afterwards two-thirds ($\frac{2}{3}$) of a grain of Calabar bean extract, the animal recovering. Eight days afterwards the same dose of extract of physostigma was given alone, and the rabbit died in seven minutes.

In a less perfectly successful case fifteen (15) grains of chloral were given to a rabbit weighing 3 lb. $\frac{1}{2}$ oz. and eleven (11) minutes afterwards two-thirds ($\frac{2}{3}$) of a grain of Calabar bean extract; the animal died in 120 minutes (two hours). This shows that death was deferred even when life could not be saved, as without the chloral death would (according to the crucial tests applied to the survivors) have taken place in from ten to fifteen minutes. Prof. Bennett's conclusions are, then—"(1) That hydrate of chloral modifies to a great extent the action of a fatal dose of extract of Calabar bean, mitigating symptoms and prolonging life. (2) That hydrate of chloral, in some cases, saves life from a fatal dose of extract of Calabar bean."

The opposite experiment was then tried of giving the Calabar bean extract before the chloral. Thus to a rabbit weighing 3 lb. two-thirds ($\frac{2}{3}$) of a grain of

Calabar bean extract were given, and three minutes afterwards fifteen (15) grains of choral. The animal was ill for eight hours but ultimately recovered. Eight days afterwards the same dose of physostigma given alone produced death in twelve minutes. In less successful cases death was delayed for a marked time. These experiments showed that chloral is less effective when given after the administration of Calabar bean, because, says Prof. Bennett, "the extract of Calabar bean produces its more severe physiological effects ten or twelve minutes after the administration of the fatal dose. In some cases the effects occur even sooner. On the other hand, a rabbit is not deeply under the influence of hydrate of chloral until fifteen or twenty minutes after it has been given. If the effects of the extract of Calabar bean appear before those of hydrate of chloral, they usually run quickly to a fatal issue, because the antagonist, hydrate of chloral, is not acting with sufficient vigor to restrain them."

Some experiments were made to ascertain if any antagonism existed betwixt morphia and Calabar bean; the results were entirely negative.

An inquiry was next instituted as to the antagonism, long said to exist, betwixt morphia and belladonna. The first step was to observe the effects of each drug given separately and then to note the effects of their combined administration. Thus "out of twenty-one experiments in which what was held to be a fatal dose

of meconate of morphia was followed by a dose of sulphate of atropia, six recovered. When the crucial test was applied to these six rabbits, six days later, by injecting ten (10) grains of meconate of morphia without sulphate of atropia, four died and two recovered." The effect of the atropia was to contract the dilated bloodvessels; as was well seen in the vessels of the ear, at the same time that the contracted pupil dilated. One of the most successful of these experiments went as follows. Ten grains of meconate of morphia were given to a rabbit weighing 3 lb. 9½ oz. and two and a half (2½) minutes afterwards a grain and a half (1½) of sulphate of atropia. The animal recovered after an illness of three hours. Six days afterwards it died in 110 minutes from the same dose of meconate of morphia given alone. On reversing the experiment it was found that out of eleven instances in which a dose of sulphate of atropia had been given previous to what was held to be a fatal dose of meconate of morphia, seven recovered. Of these seven four succumbed to the crucial test.

One of the most successful experiments was this. To a rabbit weighing 3 lb. 11½ oz. two (2) grains of sulphate of atropia were administered and seven minutes afterwards ten (10) grains of meconate of morphia, the animal recovered; but six days afterwards died of the same dose of meconate of morphia given alone.

A series of experiments were made to test the influ-

ence of atropia upon large doses of the meconate of morphia, and in every case death was postponed thereby. Thus to a rabbit weighing 3 lb. $8\frac{1}{2}$ oz. two (2) grains of sulphate of atropia were given at an interval of two minutes after twelve (12) grains of morphia had been injected: death did not take place for 110 minutes. Much the same results were attained when the morphia was given after the sulphate of atropia. Where larger doses of atropia were used with smaller ones of morphia death occurred after about the same lapse of time: indeed in some cases death seems to have been accelerated by the proportions used.

This antagonism of morphia and belladonna had previously to the formation of this Edinburgh Committee been made the subject of experiment by Dr. John Harley in England and by Weir Mitchell, Keen, and Morehouse in America; the conclusions arrived at not being in harmony with each other. Dr. Harley thought that atropia relieved the syncope produced by opium very perfectly; while the American observers found that the different rates at which these agents affected the system made it difficult to estimate the results exactly. They found that morphia did not prevent or interfere with the influence of belladonna upon the pulse. As regards the toxic effects on the cerebral organs, the two agents were mutually antidotal. Prof. Bennett tested this last antagonism by experiments on dogs.

One of the most successful experiments was as follows. To a dog weighing 14 lb. two and a quarter ($2\frac{1}{4}$) grains of meconate of morphia together with two-thirds ($\frac{2}{3}$) of a grain of sulphate of atropia were simultaneously administered. The coma was disturbed by delirium during the first two hours, but after that it went on for other four and a half hours undisturbed, after which the animal recovered. After ten days the morphia was given alone, in an hour the animal was comatose, in which state it lingered for ten hours before it died.

This experiment was repeated on a dog weighing $13\frac{3}{4}$ lb. For the first three hours it was chiefly under the influence of the atropia, rocking its head about, with dilated pupils and a fast pulse, after that it went into coma but ultimately recovered. Ten days afterwards the morphia was given alone; in an hour and a quarter the animal became comatose, and died ten hours afterwards. Thus the antagonism was demonstrated generally and the effects upon the cerebrum in particular.

Some points for consideration in the antagonism of morphia and atropia will require discussion in the latter—the practical portion of this essay; where attempts to utilize this antagonism will be considered. The results arrived at by several inquirers will then be compared; so that the work of Prof. Bennett may be proceeded with without break or interruption at present.

The next investigation proceeded with by the Edinburgh Committee was one to ascertain the relations of morphia to the different vegetable principles, thein, caffeine, cocoaine, and guaranine: and to test for any antagonism that might become manifest during the inquiry. This branch of the investigation was carried on by Dr. Alexander Hughes Bennett, who found that the minimum lethal dose of meconate of morphia in cats weighing about 4 lb.12 oz. was one and a quarter ($1\frac{1}{4}$) grains. For a cat of like weight six (6) grains of theine was a dose sufficient to cause certain death. He then performed some experiments with the minimum fatal dose of each drug given simultaneously. The majority died either of the morphia or the theine; but a number recovered perfectly, demonstrating a distinct antagonism to exist within certain limits. The smallest lethal dose of caffeine he found to be about six (6) grains for a cat about 5 lb. He then gave the lethal dose of meconate of morphia to cats and with it three or four grains of caffeine. A certain proportion recovered, after prolonged stupor; and of these a number succumbed to the crucial test of an equal quantity of morphia given alone eight days afterwards. It was also found that guaranine modified the action of morphia to some extent, but not markedly.

A series of experiments were then made to test the action of strychnine and Calabar bean given simulta-

neously. We saw before that the minimum lethal dose of strychnine was one ninety-sixth ($\frac{1}{96}$) of a grain for a 3 lb. rabbit. It was found that whenever a one-hundred-and-twentieth ($\frac{1}{120}$) of a grain of strychnine was given to a rabbit weighing 3 lb. $8\frac{1}{4}$ oz. along with one-third ($\frac{1}{3}$) of a grain of extract of Calabar bean the animal died in an hour. Now the minimum dose of extract of Calabar bean given alone is 1.2 grains (Fraser) for every three pounds, or Dr. Cook's extract (used by Bennett) three-quarters ($\frac{3}{4}$) of a grain. Thus it was found that less than the minimum lethal doses of strychnine and Calabar bean given together cause death. This fact is one which has been found by all experimenters almost, viz., that less than the minimum lethal doses of two drugs, which modify each other's action, given simultaneously, will in certain cases not successfully antagonize each other but will cause death. This matter will be referred to again in the latter section of this essay.

Prof. MacKendrick conducted a series of experiments to test the antagonism of bromal hydrate (a more potent substance than chloral hydrate) and atropia. He found that for a rabbit weighing about 3 lb. 10 oz. four (4) grains of bromal hydrate was a lethal dose. He then tried the effects of the simultaneous injection of bromal hydrate and sulphate of atropia. Thus to a rabbit weighing 3 lb. 12 oz. four (4) grains of bromal hydrate were injected along with one and a half ($1\frac{1}{2}$)

grains of the atropia. The result was recovery; the same rabbit dying in twenty (20) minutes three days afterwards of the same dose of bromal hydrate. The converse did not hold good, and the injection of bromal hydrate was powerless to avert death when given after a lethal dose of atropine.

The next most important series of experiments illustrating antagonism was performed by Dr. Crichton Browne at the West Riding Asylum, Wakefield; who was inspired by Prof. Bennett's report to test the action of picrotoxine, the active principle of cocculus indicus. Cocculus indicus had long been used by poachers to poison fish with, rendering them drunk and incapable so that they gather to the shore and are easily caught in hand-nets. This property of producing drunkenness had attracted the attention of dishonest brewers who used it to economize malt, and to give to cheap and bad beer a sufficiency of intoxicating property to render it salable. Having observed its effects on rabbits and guinea-pigs, Dr. Browne found that it produced in toxic doses very pronounced symptoms; acting chiefly upon the cerebro-spinal centres, and producing clonic spasms, the dorsal muscles of the trunk being strongly affected. Bearing in mind what Prof. Bennett had observed of the power of chloral to control the convulsions caused by strychnia-poisoning, Dr. Browne determined to test its efficacy upon picrotoxine poisoning. Having found that the minimum lethal dose of picro-

toxine for a rabbit weighing 3 lb. was one-twentieth ($\frac{1}{20}$) of a grain, he administered along with this ten (10) grains of chloral in one case, with the result that though the rabbit was very ill it perfectly recovered. These experiments are very graphically described in perspicuous language, and are thus rendered doubly interesting. It appears that the chloral held the animal quiescent until the effects of the picrotoxine wore off. Thus without the chloral the rabbit would have died in betwixt eighty and ninety minutes with certainty. With the chloral the animal was very ill, but after the lapse of ninety minutes it was able to get up and get away to a corner. Two hours after the injection it was comparatively quite well and feeding.

Dr. Browne varied his experiments, and found that even so much as one-fourth ($\frac{1}{4}$) of a grain of picrotoxine could be survived if accompanied by a full dose (21 grains) of chloral hydrate; and that even with half ($\frac{1}{2}$) a grain death did not take place for six (6) hours. No rabbit was ever found to survive one-sixteenth ($\frac{1}{16}$) of a grain of picrotoxine alone, so that no crucial test was applied to those rabbits which survived the first experiment of the co-administration of picrotoxine and chloral. To those rabbits to which one-twentieth ($\frac{1}{20}$) of a grain of picrotoxine was given with chloral, the same dose was given a week later with the result that the rabbits died within (90) minutes after the injection of the picrotoxine.

It appears that when full doses of picrotoxine ($\frac{1}{8}$ of a grain) and of chloral hydrate (15 grains) were given together, the animal in about twenty-five minutes was wrapt in a deep chloral sleep broken by clonic picrotoxine spasms at intervals. These clonic spasms occurred about every three (3) minutes, the animal being fast asleep during the intervals. The same phenomena were observed with guinea-pigs. It was found that one-thirtieth ($\frac{1}{30}$) of a grain of picrotoxine was sufficient to kill with certainty a guinea-pig weighing a pound and a half, showing that guinea-pigs are not quite so susceptible to the poison as rabbits. When this lethal dose was combined with five (5) grains of chloral hydrate, the guinea-pig recovered. The chloral sleep was broken by twitchings and imperfect convulsions. Even one-sixteenth ($\frac{1}{16}$) of a grain was survived by a guinea-pig weighing only 1 lb. 2 oz. when seven (7) grains of chloral hydrate were given at the same time. This was twice the minimum lethal dose. As much as one-eighth ($\frac{1}{8}$) of a grain was survived ten hours and a half by a guinea-pig weighing 1 lb. 7 oz. when eight (8) grains of choral hydrate were simultaneously administered with it.

Having clearly proved the antagonism existing betwixt these two agents, Dr. Browne then experimented to ascertain how long the administration of the chloral might be delayed and yet a fatal result be averted. He found that when a twentieth ($\frac{1}{20}$) of a grain of picro-

toxine was given to a guinea-pig weighing about 1 lb. 9 oz., the minimum lethal dose being one-thirtieth ($\frac{1}{30}$) or one and a half times the smallest fatal dose, and then seven (7) grains of chloral hydrate given within half an hour, the animal survived. When the chloral was not given till thirty-eight (38) minutes after the picrotoxine a fatal result followed.

The next point to be settled was this: "Could the lethal action of chloral be as certainly arrested and modified by picrotoxine, as that of picrotoxine had been shown to be by chloral hydrate?" The Edinburgh Committee had determined that twenty-one grains for a 3 lb. rabbit, or seven grains per lb. of body weight, was the minimum lethal dose of chloral. Taking this as a basis, twenty-three (23) grains of chloral were given to a rabbit weighing 3 lb. 4 oz. and with it one-fortieth ($\frac{1}{40}$) of a grain of picrotoxine, the sleep was but slightly disturbed and the animal recovered. Increasingly larger doses were given of each agent until it was found that even 40 grains of chloral could be survived by a rabbit weighing 2 lb. 9 oz. when one-twenty-fifth ($\frac{1}{25}$) of a grain of picrotoxine was also given with the chloral. The crucial test was used in this series of experiments, with the result that it was found that the rabbits recovered from doses of chloral up to 35 grains as surely without the picrotoxine as with it; their sleep being sound and undisturbed instead of broken—that was all the difference. It be-

came necessary then to test the minimum lethal dose of chloral upon the Yorkshire rabbits, when it was found that twelve (12) grains to the pound weight was the lowest certainly fatal dose. This discrepancy was due to the fact, in all probability, that Dr. Browne's experiments were performed in a room with a temperature of 56° Fahr. and the animals were laid before the fire and on cotton wool; the effects of temperature upon chloral poisoning having been clearly ascertained by Dr. Lauder Brunton and others. So another set of experiments were made on this new basis of twelve (12) grains of chloral to the pound of body weight, when it was found that small doses of picrotoxine had little or no effect upon the final result. Then larger doses of picrotoxine were tried, but without the desired result. Even as much as one-fourth ($\frac{1}{4}$) of a grain of picrotoxine failed to avert death after forty (40) grains of chloral had been administered.

Nevertheless the picrotoxine was not without effect. "It limited the depth of the chloral narcosis, and broke in upon it occasionally by intervals of semi-wakefulness, in which there were various spontaneous movements." It also prevented to a considerable extent the fall of temperature and of the respirations occasioned by chloral. Thus to one rabbit weighing 3 lb. and $1\frac{1}{2}$ oz. thirty-five (35) grains of chloral were given alone, and its temperature fell from 100·4° to 85·8°, and its respirations per minute from 60 to 16,

when it died. To another rabbit weighing 2 lb. 14½ oz. also thirty-five (35) grains of chloral were given, but with this dose was given one-twenty-fifth ($\frac{1}{25}$) of a grain of picrotoxine. Its temperature fell from 100° to 90° and its respirations from 72 to 52, when it gradually recovered. This indicates a distinct antagonism in several directions.

Some experiments with picrotoxine and chloral hydrate were next made on cats, with unsatisfactory results. Some further experiments promised by Dr. Crichton Browne will probably throw some light upon the different effects upon cats to rabbits and guinea-pigs. Already Dr. Browne has seen that the effects of chloral are more pronounced upon animals with convoluted than with smooth brains. Idiots take larger medicinal doses of chloral than other persons, whether sane or insane. The next series of experiments on any extensive scale was made by myself.

I commenced by following out some primitive experiments on the frog illustrating the antagonism of aconite and digitalis, performed in 1870. It became necessary in the first instance to ascertain the minimum lethal dose of these drugs in the animals to be operated upon. It was found that aconitine as prepared by Messrs. Morson was a very deadly poison, one three-hundredth ($\frac{1}{300}$) of a grain being fatal to a rabbit weighing 3 lb., while one four-hundredth ($\frac{1}{400}$) was sufficient for a rabbit weighing 1½ lb. The guinea-

pig was even more susceptible to this agent, and one twelve-hundredth ($\frac{1}{1200}$) of a grain was found sufficient to kill with certainty a guinea-pig weighing $1\frac{1}{2}$ lb. A cat weighing 3 lb. was killed in 55 minutes by one-sixtieth ($\frac{1}{60}$) of a grain of aconitine. Of digitaline it was found that about one (1) grain (S. and H. Smith's) to the pound weight was the minimum fatal dose. Digitaline and aconitine were then simultaneously administered with little positive result, the action of the aconitine being little influenced thereby. When however the digitalis was given some (from 5 to 9) hours before the aconitine a distinct protective influence was exercised. Thus to a rabbit weighing 3 lb. 1 oz. one grain and three-tenths ($1\frac{3}{10}$) of digitaline were administered and five hours afterwards one two-hundredth ($\frac{1}{200}$) of a grain of aconitine (or one-half more than the lethal dose), the rabbit recovered. A week afterwards the same dose of aconitine was given alone, death being the consequence in fifty minutes. But when given at a less interval death was not only not averted, but the poison seemed positively intensified. This curious fact about drugs ordinarily antagonistic has been noted by several other experimenters. Finding the antagonism of aconite and digitalis in the rabbit thus unsatisfactory I turned my attention to belladonna, and tested for any antagonism existing betwixt it and aconitine. Thus to a rabbit weighing 2 lb. 6 oz. I gave three (3) grains of atropia and six

minutes afterwards one three-hundredth ($\frac{1}{300}$) of a grain of aconitine: the animal survived. A week afterwards the same rabbit had the aconitine alone and died in two hours and a half.

Then small non-fatal doses of aconitine were tried upon lethal doses of atropia with negative results. It was next determined to try the effects of small doses of atropia 4 grains (about one-fifth of the lethal dose—20 grains) upon lethal doses of aconitine previously administered. The results were very striking. Thus to a rabbit weighing 2 lb. 4 oz. one three-hundredth ($\frac{1}{300}$) of a grain of aconitine was given, and two minutes afterwards four (4) grains of atropine, the animal recovered.

To another rabbit weighing 2 lb. 9 oz. also one three-hundredth ($\frac{1}{300}$) of a grain of aconitine was given and 13 minutes afterwards four (4) grains of atropia; the animal recovered. When put to the crucial test of the same dose of aconitine alone a week afterwards the animals all died. It was found however that if the administration of the atropia was delayed beyond 16 minutes it was powerless to arrest the lethal action of the aconitine. "It is very interesting to see how the rabbits under the influence of aconitine, but protected by the previous administration of digitaline, or the previous or subsequent administration of atropine, will become exceedingly ill, but, instead of a fatal, there

follows a process of rapid recovery." (*Brit. Med. Journal*, Aug. 4, 1877.)

The results of this series of experiments were so striking and satisfactory that it was determined to try the effects of atropine on chloral hydrate in lethal doses. The results were not very encouraging. The atropia certainly prolonged life very considerably, but that was all. The influence exercised by atropia over chloral poisoning fell far short of that which Prof. Hughes Bennett had found strychnia to exercise. Indeed he found strychnia to antagonize the chloral successfully in the majority of instances. The opposite experiment of the effect of non-fatal doses of chloral upon lethal doses of atropia gave also negative results.

The next experiment devised was to test the effect of lethal doses of strychnine upon lethal doses of aconitine. Thus to a rabbit weighing 2 lb. 9 oz. one-three-hundredth ($\frac{1}{300}$) of a grain of aconitine was administered and, after an interval, one fiftieth ($\frac{1}{50}$) of a grain of strychnia: it recovered. This dose of strychnia is twice the minimum fatal dose according to Prof. Bennet. The antagonism of strychnine and aconitine is very marked, so far as the influence of strychnine upon lethal doses of aconitine is concerned; but whether aconitine exercises a favorable influence over strychnine in lethal doses there is yet no evidence to show—these experiments being cut short abruptly at

this very interesting point by the passing of the Vivisection Act.

Digitalis exercised none or but little influence over the failure of the respiration induced by the aconite. The lesson of these experiments then is chiefly that aconite kills by paralyzing the respiration, while atropine and strychnine, which act very powerfully upon the respiratory centres, were potent to prevent death. The effect of digitaline given hours before the aconitine illustrates how closely the respiration is linked with the circulation, and how difficult it will be to effectually separate the action on the respiration from the effects upon the circulation, in differentiating the action of these two powerful toxic agents.

Such are the main experiments which have been made for the purpose of testing the antagonism existing betwixt certain potent remedial agents. A few less important inquiries may be added.

Prof. Sydney Ringer having observed the antagonistic or rather opposite action of belladonna and jaborandi upon the skin and salivary glands, had a case of atropia poisoning brought into his ward in University College Hospital. It was a boy who had taken one (1) grain of atropia five (5) hours previously. Half a drachm of jaborandi-leaves was given in infusion and in a quarter of an hour his mouth had become much less dry; and in an hour he was sweating freely and his mouth was normally moist. This was satisfactory,

so Prof. Ringer followed it up by an experiment. He gave one-third ($\frac{1}{3}$) of a grain of pilocarpine, the principle of jaborandi, to a patient subcutaneously; and after free salivation and sweating had been established, he injected subcutaneously one-hundredth ($\frac{1}{100}$) of a grain of atropine. In five minutes the skin was quite dry. A couple of cases of belladonna-poisoning shortly after this again enabled him to test the antagonism existing between these two agents.

On Dec. 24, 1875, J. C., ætat 64, had swallowed from 1 to 2 drachms of belladonna liniment at 12.30. An hour after this he was brought to the hospital and an emetic administered. At 2.50 the pulse was 100, and the respirations 22. The legs became rigid, and delirium set in in five hours. During this time jaborandi had been given. At 2.15 one-third ($\frac{1}{3}$) of a grain of pilocarpine was administered; at 3.15 another third of a grain; at 3.50 another third; and at 5 a fourth third of a grain; so that in all the man got $1\frac{1}{3}$ grains of pilocarpine. This modified the symptoms, and the man recovered.

In a second case a girl of four drank some belladonna liniment (it was said by her mother about half an ounce) at 12.30, September, 1875. One grain of pilocarpine was injected at five different times; the first 25 minutes, the last $8\frac{1}{2}$ hours, after the taking of the poison. A decided influence was produced by the pilocarpine, but the details are not given at length.

Some experiments on the antagonism of strychnia and hydrocyanic acid were conducted last year by Dr. Lauder Brunton, F.R.S., and Mr. W. J. S. Ladell and Mr. W. Outhwaite. After relating the experiments performed by them, they conclude their report: "Although hydrocyanic acid may somewhat lessen the tetanic convulsions produced by strychnia, it cannot be employed as an antidote to that poison with any hope of success." It seems unnecessary to give any account of these negative experiments.

A series of experiments as to the antagonism of strychnia and nicotin have been conducted by Dr. Francis L. Haynes in Philadelphia quite recently. He found that when a small dose of nicotin (from $\mathfrak{m}_{\frac{1}{100}}$ to $\mathfrak{m}_{\frac{1}{60}}$) was injected into a rat, its breathing became labored, and signs of general prostration were induced. After larger doses (from $\mathfrak{m}_{\frac{1}{60}}$ to $\mathfrak{m}_{\frac{1}{40}}$) convulsions occurred. The respiration after each convulsion ceased for several seconds, and sometimes for more than a minute. When death occurred it was through failure of the respiration. The heart invariably continued to beat for a time after the respiration had ceased. The minimum fatal dose of nicotin for rats weighing $10\frac{1}{4}$ oz. was about $\mathfrak{m}_{\frac{1}{150}}$. The same profound disturbance of the respiration was found to take place in rabbits, for which animals one-eightieth ($\frac{1}{80}$) of a grain to the pound weight was a lethal dose. One curious fact has been elicited by Dr. Haynes's

experiments, and that is this. An animal—rabbit, cat, or dog—will survive a certain dose of nicotin; and after some days a certain dose of strychnia; but if the same doses of the two agents be given together a week afterwards, death occurs swiftly with powerful tetanic convulsions. The fact of the combination of two toxic agents in non-lethal doses causing death rapidly has been noted by other observers, and is a troublesome fact to be overcome in estimating the practical outcomes of these varied experiments as to the antagonism of toxic agents. Sufficient, however, has been done to point to some very valuable conclusions of which some account will next be given. The provisions of the Vivisection Act have arrested the pursuance of these inquiries in Great Britain, but a grand field is opened up to foreign inquirers, in which they will gather up many important facts, and add much to the resources of practical medicine.

The practical outcomes of the experiments related above, taken in conjunction with the results of other inquiries will next be given.

CHAPTER II.

PRACTICAL INQUIRY.—ACTION OF DRUGS CHIEFLY AS ASCERTAINED BY EXPERIMENT—CALABAR BEAN.

The therapeutic usefulness of Calabar bean is yet to be thoroughly investigated, and especially its effects on the circulation and respiration. So far its action on these systems has only led to its use in the treatment of the general paralysis of the insane. In Prof. Frazer's experiments could be seen the lowering of the pulse-rate and respiration by Calabar bean; and he further observed the depressant action upon the spinal motor centres exercised by this agent. Dr. Crichton Browne noted these actions ascertained by experiment, and conceived the utility of the drug in controlling the violent outbreaks of excitement to which sufferers from general paralysis are so subject. The muscular action of these insane paralytics in their fits of excitement, which occur in the early stages, is excessive, and their violence such as to lead to serious conflicts and trials of strength betwixt them and their attendants, often resulting in injury, sometimes serious to both parties. Accordingly he administered Calabar bean to these

patients during their periods of excitement, and found the results to be satisfactory in the highest degree. The drug calmed the patients generally by its effects upon the circulation and respiration, while its action on the spinal centres and the muscular system deprived them to a great extent of that muscular force which is a source of danger to themselves as well as those restraining them. Not only were good effects immediately produced during the attacks of maniacal excitement, but the use of the drug in many instances exercised a pronounced control over the progress of the malady, retarding it markedly; and in a few cases apparently arresting it for a while entirely.

This is a very excellent illustration of the power of knowledge arrived at by experimentation to aid practical medicine. Calabar bean has not yet been extensively used in asylum practice, as chloral exercises an allied, if not an identical, action, and is a drug very easily handled. If chloral had not been discovered, probably Calabar bean would have been largely resorted to in cases of acute mania and other forms of excitement in lunatics.

In speaking of Prof. Frazer's researches Wood says: "These researches ought certainly to be carried further, to discover if possible why it is, or rather how it is, that atropia acts as the antidote of Calabar bean. It will probably be found that the mydriatic saves life by its stimulant action upon the respiratory centres."

From the actions of Calabar bean and chloral it will be seen that they are both drugs unsuited to cases where the respiration is involved, and especially where both the respiration and the circulation are implicated, as tending to increase the probability of failure in these systems, and so of causing death. But in other conditions, where there is vascular excitement and corresponding respiratory activity, the persistent use of these depressant remedies is admissible, and often may be resorted to with advantage. Thus Dr. Browne found Calabar bean not only to diminish the violence of the outbreak of general paralytics, but that it also exercised a good effect over the progress of many cases, especially in the early stages. Now in its early stages general paralysis is usually accompanied by improved nutrition, the patient is stout and plump, and almost invariably there is hypertrophy of the heart, with accentuation of the aortic second sound. Under such circumstances the persistent use of Calabar bean was rather indicated than otherwise; for its action on the circulation, aided probably by its action on the respiration, retarded those morbid changes which usually go on swiftly, and destroy the patient in a short time. This is rendered the more probable, that these morbid changes are dependent upon an abnormally vascular condition of the encephalic contents; while Calabar bean lowers the arterial circulation within the cranium as well as elsewhere.

CHLORAL HYDRATE.

The action of chloral hydrate has been largely elucidated by experiment. It is generally known that chloral is an hypnotic of great value, especially where the insomnia is not due to pain. But where there is insomnia associated with excitement, and especially vascular excitement, chloral is the hypnotic *par excellence*. Chloral produces a double effect, viz., an action on the brain cells, and another upon the circulation, betwixt which sleep, almost identical with natural sleep, is produced. It is thus adapted for conditions of pyretic insomnia with vascular excitment. Chloral lowers the heart's action, so that the circulation is rendered less active ; while its effects upon the cutaneous vessels is to dilate them, and by this double action of impaired chemical interchanges from lowered circulatory activity, and increased mass of blood in the external, or heat-losing area of the organism, the body-temperature is much reduced. So much is this the case that the lethal dose of chloral in rabbits is much affected by the surrounding temperature ; is less in cold weather than in warm ; and a much larger dose still is required to produce toxic results if the animal be laid before the fire, or wrapped in cotton wool during its deep chloral sleep (Brunton). In addition to its action upon the circulation, chloral powerfully affects the respiration. In speaking of chloral poisoning,

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Wood says; "The immediate cause of death is generally a paralytic arrest of respiration: but in many cases there appears to be a simultaneous arrest of the cardiac action, and it is very possible that fatal syncope may at times occur." This action of choral it is well to bear in mind, and it should never be given, or if so only with the greatest caution, in cases where the respiration and circulation are both involved, as in chronic bronchitis with dilatation of the right heart, especially when there is also present emphysema; in cases of valvular disease of the heart, etc., etc. Negative lessons are often of as much value as positive lessons; and in the practice of medicine it is often as important to know what to avoid in prescribing, as what to adopt. Almost all potent remedies have actions which render caution necessary in using them, and of no drug is this more true than of chloral. In the sleeplessness of valvular disease of the heart chloral is very dangerous, and is apt to produce fatal depression of the circulation and respiration. This is no more than what we might expect from its action as revealed by experimentation. In cases of lung disease, where the heart is only affected secondarily, but when the right ventricle is being severely taxed, chloral is equally contra-indicated.

When it becomes desirable, on the other hand, to diminish the energy of the respiration from any cause, chloral will be found a useful agent. In the experi-

ments of Prof. Bennett it was found that the potency of chloral to arrest strychnia poisoning was largely due to its effects upon the respiration. He says of chloral given at an interval after a fatal dose of strychnia: "If the physiological effects of strychnia showed themselves in a marked way before the animal came under the influence of the chloral hydrate, death was liable to ensue from asphyxia due to tetanic spasm of the muscles of respiration. The sooner the chloral hydrate was given after the administration of strychnia, the more certain was the animal to survive." Macnamara has found chloral exceedingly valuable in the treatment of tetanus, and records that of twenty cases in India, all traumatic, no less than seventeen were saved. His idea was to use it as an hypnotic; but the effects upon the respiration must have had much to do with the results. In laryngismus stridulus, in asthma, and in whooping-cough, chloral has been used with considerable success.

So far, however, chloral has been given merely in an empirical manner; but as our knowledge of the effects of agents upon the respiration increases, so may we hope to wield chloral and allied agents, in a rational and enlightened manner, with good effects in diseases of the respiratory organs. Already the negative lesson of under what circumstances to avoid it is becoming very intelligible. A case in point suggests itself. A patient was taken into the West London

Hospital with emphysema and aortic stenosis. In spite of rest, digitalis, and ammonia, he was liable to attacks of dyspnœa, which had come on since his admission into hospital. On searching for an explanation, it was found that the house surgeon had benevolently prescribed chloral for the sleeplessness complained of. This was at once stopped, and the attacks of dyspnœa never returned, though the man gradually sank. This case was most instructive.

Chloral acts upon the respiratory centre in all probability, as the frequency of the breathing is diminished by it, even after section of the vagus.

A case of chloral poisoning successfully treated will serve to illustrate still more distinctly the action of chloral, and to demonstrate the utility of strychnia as an antagonist. Dr. Levinstein had a case of a man poisoned by six drachms of hydrate of chloral. Remembering the experiments of Liebreich as to the antagonism of chloral and strychnia, the latter drug was injected to the extent of producing twitching of the muscles; and artificial respiration was maintained. The heart had ceased to beat, and the temperature had fallen to 92°, yet the man made a perfect recovery. More recently, two cases of strychnia poisoning have been recorded where chloral gave marked relief. (See Chapter VI.)

Ringer gives a caution about the use of chloral in patients with lung and heart-mischief combined; and

says that an ordinary dose, besides drowsiness, may produce delirium and a notable lividity, lasting for days. In regard to the action of chloral upon the cerebral hemispheres, Dr. Crichton Browne has made an interesting observation. He says: "The energy of the action of chloral hydrate, as measured by its minimum fatal dose, is in proportion to the development of the cerebral hemispheres." This experience of its effects upon animals is in full accordance with his clinical experience of chloral. He says: "In microcephalic idiots, again, I have noticed that a proportionately larger dose of chloral hydrate is requisite to induce its physiological effects than in persons with fully-developed brains." This observation is of practical value in prescribing chloral for persons of high cerebral development. It further throws a light upon some cases of fatal poisoning with comparatively small doses of chloral. It would appear that chloral is most dangerous to the most intellectual.

MORPHIA.

In considering the action of morphia here, the inquiry will only extend so far as its actions have been elucidated by the foregoing experiments. Wood says: "Death occurs from opium, in the great majority of cases, by failure of the respiration; and that such failure is due to a direct action of the poison upon the respiratory centres in the medulla is proven by the

fact that morphia affects the breathing of dogs and rabbits whose pneumogastrics have been cut, as much as it does those whose nerves are entire." And again: "To maintain respiration is the ultimate object of all the measures which are commonly undertaken for the purpose of arousing the system in opium-poisoning," and advocates resort to artificial respiration in cases where the respiration is failing. From what we have seen of the action of belladonna upon the respiratory centres, the antagonism betwixt it and morphia, which has been noted by so many different observers, becomes readily intelligible. Prof. Hughes Bennett also tested the antagonism betwixt morphia and theine and caffeine, and found that these agents were antagonistic to morphia. He says: "The action of the one substance modifies that of the other, and may even save life from a fatal dose of either substance."

These vegetable principles act like strychnine in obstructing the respiration by inducing spasm of the respiratory muscles. On the other hand, morphia kills by bringing these muscles to a standstill in paralysis; and thus we can understand how these agents antagonize each other. Of course, it is not for one moment assumed that this antagonism is confined solely to the action upon the respiration. The interest of these antagonisms lies around the use of morphia in the treatment of diseases of the respiratory organs. Thus in bronchitis, for instance, morphia is a very dangerous

drug to use. It not only arrests secretion, and thus increases the difficulty of expectoration and respiration, but its action upon the respiratory centres is such as to paralyze them when already embarrassed. It is useful in the hacking cough of phthisis, where cough is excited by the presence of diseased masses in the lungs; and where the cough is distressing and yet useless, and incapable of getting rid of the source of irritation. Here it is necessary to stop the reflex mechanism of cough. This morphia does most effectually. It is noted, however, that morphia is not an unalloyed good in such cases. In addition to its action in destroying the appetite and locking up the bowels, it lowers the respiration while checking the cough. When under the influence of morphia, the patient sweats profusely, and to the extent of producing much exhaustion. Morphia acts upon the skin, as is well known, and it aggravates the night sweats to which such patients are subject. I have combined belladonna with morphia, and found that this checks the sweats, while the morphia allays the cough; the action of morphia upon the cough not being interfered with by the co-administration of the belladonna; indeed, belladonna affects the terminal ends of the vagi in a manner which aids the action of morphia. The effect of the belladonna is not confined to the skin, but it influences the respiration favorably. Weir Mitchell, Keen, and Morehouse found that morphia had no in-

fluence over the changes in the pulse produced by atropia. They did not note the respiration. They further go on to say: "As regards toxic effects on the cerebral organs, the two agents are mutually antidotal; but this antagonism does not prevail throughout the whole range of their influence: so that, in some respects, they do not counteract one another; whilst as regards one organ—the bladder—both seem to affect it in a similar manner."

Now Lauder Brunton says of belladonna: "Atropia stimulates the respiratory centre, but at the same time it lessens the irritability of the sensory nerves of the lung, and will thus, while increasing respiratory efforts, diminish the sensibility of the lung to irritation." Thus it would seem that the addition of belladonna to morphia in such cases, whilst it arrests the profuse perspiration, will add to the effects of the morphia upon the cough. The effect of morphia is to lower the respiration, while influencing the reflex mechanism of cough. Belladonna diminishes the sensibility of the lungs to irritation, and so aids the action of the morphia. But morphia lowers the respiration at the same time, while belladonna stimulates it. Consequently we can comprehend how belladonna is useful in this combination. It not only arrests the perspiration, but it also maintains the respiration. When morphia is given alone the patient sinks into a deep sleep and perspires very freely. If he keeps awake, still coughing, the

perspirations are not so profuse; this is a matter of clinical observation. It may be that in partially paralyzing the respiration the opium calls out the cutaneous respiration—for the association betwixt diseases of the respiratory organs and the skin is well known (Carpenter, *Human Physiology*, § 309), and the free action of the skin compensates for the imperfect action of the ordinary pneumonic respiration. Now if belladonna stimulates the respiratory centres, it probably prevents this paralyzing action of the opium, and so partly does away with the necessity for profuse perspiration, as well as exercising direct effects upon the sudoriparous glands. Certain it is that the combination of morphia and belladonna in the treatment of the severe harassing cough of phthisis is most useful.

This consideration of the effects of morphia and belladonna upon the respiration leads us up to a further advance in our selection of remedies in the treatment of diseases of the respiratory organs. It teaches what to avoid in certain cases; how and why we should not give opium or morphia when the respiration is failing; and it enables us to understand why and wherefore we should give certain medicines in other conditions, as belladonna in asthma, and why we should give ammonia and strychnine when the respiration is severely taxed or failing. It enables us, indeed, to see more clearly how to wield our agent in practice,

and tells us what to avoid, as well as what to attempt, in our therapeutic efforts.

The effects of morphia, chloral, and bromide of potassium in convulsive affections of the respiratory organs will be considered in a subsequent portion of the essay.

We will now proceed to consider the action of agents which are stimulants to the nerve centres, either all or some of them.

BELLADONNA.

Experimentation has done much to bring out some actions of belladonna which had before been but imperfectly appreciated. The experiments of Prof. Frazer show the effects of belladonna in arresting death from Calabar bean in lethal doses. When the physostigma was administered the number of cardiac beats and the respiration fell very markedly; but upon the injection of belladonna they rose, first above the normal rate, and then again fell to it, and remained there; the animal gradually recovering. For instance, previous to the administration of the physostigma the heart's contractions of a rabbit were 40, and the respirations 20, per ten seconds. After the administration of the Calabar bean the heart's contractions gradually fell to 32, 22, and ultimately 11, in the same time; reaching the lowest point twenty-eight minutes after the injection of the physostigma. Some

sulphate of atropia was then injected, and in one minute the heart's contractions had risen to 56 per ten seconds; in seven minutes to 60, about which it remained for an hour and a half, after which it fell to its usual rate. The respirations fell from 20 to 16 in three minutes after the injection of the physostigma; in twenty-eight minutes "there were only infrequent labored respirations occurring at irregular intervals," the number not being given. After the injection of the atropia the respirations rose to 15 in two minutes; in six minutes to 20 again; and in an hour and a half had settled to 15 per ten seconds. The observations of Prof. Bennett in his report to the British Medical Association, on the antagonism of belladonna and Calabar bean, and those of myself on the antagonism of belladonna and aconite, are not nearly so close and exact as those of Prof. Frazer, which are most precise. My own observations go so far as to note that in aconite poisoning the respirations fail, and that digitalis did not affect the respiration sufficiently to prevent this, while belladonna did. After the administration of belladonna the respirations, which had been failing under the aconite, recovered again until they reached a normal point.

Now these experiments point to the effect of belladonna upon the respiratory centres. When death is approaching from paralysis of the respiration induced by a poisonous agent, belladonna restores the respira-

tory efforts, and so saves the animal from death. Side by side with this action stands the well-known empirical facts of the utility of belladonna in different affections of the respiratory organs, especially neurosal disturbances. Thus belladonna was lauded by Hyde Salter in the treatment of asthma, and is highly spoken of by Meigs and Pepper for the treatment of whooping-cough in children. Wood also states that belladonna has been found useful in the treatment of neurosal cough, in hiccough and affections in which the nervous mechanism of the respiration is involved. It cannot be a mere coincidence this empirical use of belladonna in nervous affections of the respiratory organs, and its potency in preserving life when threatened by failure of the respiration in animals experimentally poisoned. There must be some distinct connection betwixt the two different sets of facts, and what it is will be set forth as explicitly as may be in a later section of this essay.

Belladonna has also an action, and a very marked one, upon the circulation. In moderate doses it raises the blood-pressure in the arteries, partly by contracting the peripheral arterioles, and partly by its direct action upon the heart. John Harley has said that in consequence of this action belladonna is the best direct diuretic for increasing the bulk of urine, that we possess. Its utility in both Calabar bean and aconite poisoning shows that it prevents cardiac paralysis, as well as acting upon the respiration. Its empirical use

in the form of a plaster in palpitation of the heart testifies to its influence over the cardiac nervous centres.

The power of belladonna to arrest death from depressant poisons, as ascertained by experiment, together with its well-known deliriant action in toxic doses, has led to its use in cases of melancholia and dementia where there is cerebral anæmia, together with a state of atony or inertia of the circulation. For the treatment of such cases it has been found useful by Hammond in America and Crichton Brown in this country. The delirium occasioned by toxic doses of belladonna is attributed by John Harley to the high blood-pressure caused by this agent. In opium poisoning there is deep sleep or coma, with a low blood-pressure. In belladonna poisoning there is no sleep, but a restless delirum with a high blood-pressure.

There seems every reason to believe that belladonna may be usefully combined with opium or morphia in those cases where it becomes imperative to give very large doses of these agents, such doses indeed as may threaten the respiration or circulation. Belladonna will maintain the actions of the centres under huge doses of morphia, without interfering materially with the effect upon the cerebro-spinal centres.

STRYCHNIA.

Strychnine is a therapeutic agent which has a very powerful action on the organism. Its effects in toxic doses are such as to direct the attention readily to its action upon the nervous system. Its stimulant properties are thus generally recognized, but we have still much to learn about its more special actions, which the foregoing experiments indicate. Its effects upon the heart as a tonic are being recognized, and it is found that the arterial blood-pressure is greatly heightened by it. This is not due to the obstruction to the blood-flow caused by the convulsions excited, for it occurs as markedly in animals whose muscles are paralyzed by curari. The small arteries have been seen to contract in strychnia poisoning, and in some cases of fatal poisoning the heart has been found rigidly contracted. That strychnia is a cardiac tonic is pretty generally recognized; but the experiments of Oscar Liebreich, of Prokop Rokitansky, of Professor Hughes Bennett, and of myself render it extremely probable that strychnine has a powerful action upon the respiration also. Liebreich and Bennett found that it exercised an influence over chloral in toxic doses, and Professor Bennett found chloral even more potent in strychnia poisoning. The effects of chloral upon the respiration are well known, and if strychnia had not antagonized its effects upon the respiration as well as

upon the heart, it seems very improbable that it could have averted death. For I found that digitalis did not avert death from aconite when given simultaneously or after the aconite, while strychnia did. The digitalis, though acting upon the heart, did not act speedily enough upon the respiratory centres, and so the animals died from failure of the respiration. It appeared however that if the digitalis was given from five to nine hours before the aconite it exercised a sufficient influence to avert death. For the purposes for which these experiments were apparently instituted viz., to find out the antagonism of aconite and digitalis in warm-blooded animals, they have failed ; but they teach a lesson in another direction of distinct value. They point out that aconite and chloral kill by arresting the respiration as much as the circulation, and that to antagonize this double action agents are required which stimulate the respiratory centres as well as the cardiac ganglia. It is clear that further experimentation in this direction is urgently required ; but the obstructions now placed in the way of experiment in Great Britian are such as to render it very unlikely that they can be carried out here, and the further elucidation of this interesting subject will fall into foreign hands. It is possible however to advance the subject to some extent by clinical observation. Clinical medicine can however be utilized, and it is found that strychnia, added to potash and expectorants, in

the treatment of chronic bronchitis with emphysema and a dilated right heart is very useful. The results of extensive observations warrant the statement that the addition of the strychnia to such a mixture was followed by increased efficiency, and in some cases by decided relief. It seems to ease the breathing, that is—the patients declared that they breathed easier and with less discomfort after taking their medicine. Of course it is much more difficult to make such observations as permit of being tabulated in striking form upon paper, on the respiration, than are practicable in noting the effect of digitalis upon the heart, and therefore only general statements can be made. It certainly on the whole seemed a desirable addition, even when digitalis had been added to the mixture previously; and reading the results by the light of the experiments given in the early section of this essay, it is not difficult to comprehend that good results in these cases should ensue from such use of strychnia. When death is induced by strychnia poisoning it is brought about by asphyxia, the muscles connected with the thorax being so spasmodically contracted in the convulsions that the respiration is arrested. That strychnia in lesser doses should act as a stimulant to these respiratory muscles is a fair induction and a feasible hypothesis; and it is certain that strychnia does not act upon the muscles directly, but mediately through the nervous centres.

In pursuance of the above idea the writer has given strychnia extensively as an agent influencing the respiration with the very decided impression that it does affect the respiration beneficially in many cases. The following case is to the point:—J. R——, 35, complained much of difficulty of breathing, with some cough without expectoration. The respirations could not be noted by the usual plan of laying the hand over the front of the chest, or of simply counting the respiratory movements. They were too slight to be detected; and it was only by stripping the man that a faint movement along the costal cartilages could be observed at each inspiratory act. The man's face was indicative of the distress he suffered from the difficulty of breathing. What was to be done for him it was not easy to see, for the respiratory sounds were feeble all over the chest, and the percussion note dull, and the diagnosis arrived at was that the case was one of general fibrosis of the lung. It was impossible to add to the thoracic space, and it was equally impossible to diminish the excessive connective tissue in the lungs. All that apparently could be done was to act upon the respiratory centres and stimulate them, just as digitalis is given to stimulate a feeble heart. Ammonia is the most powerful means of acting upon the respiration with which we are yet acquainted; so five grains of carbonate of ammonia, with fifteen drops of tincture of nux vomica, were prescribed, with the agreeably surprising result

that in a fortnight the man expressed himself so much relieved in his breathing that he wished to resume work, and has continued to do so, though with some difficulty. At the end of three months his respirations, though labored, could be counted in his clothes, like that of ordinary persons. It is not possible yet to explain completely the *rationale* of such a change, but it seems fairly attributable to the medicine in the first place. In the present state of our knowledge, at least, we can offer no explanation of the facts, except that these two agents, which exercise a powerful influence upon the respiratory centres, had rendered the act of breathing easier to the man.

But the whole question of the respiratory centre will be taken up shortly, and then the different facts of experimentation and observation may be massed together, so as to point definitely to some conclusions which will not be without their practical value.

This use of strychnia in affections of the respiratory organs is not novel. The subject has attracted the attention of Dr. Thorowgood in his work on Asthma. He says: "In cases of paralytic and emphysematous asthma the real and permanent good that can be done with the tincture of nux vomica, and with very small doses of strychnia, is unmistakably great. The tincture may be given in doses of from three, eight, or ten drops, and the liquor strychniæ of the British Pharmacopœia in doses of two to five drops." Dr. Thorow-

good does not distinctly formulate any hypothesis as to the action of strychnia; but in speaking of complicated asthma, he says: "Sedatives at night do not interfere with other remedies during the day; but it is well not to be in too great a hurry to resort to them, for it is not uncommon to find such a medicine as nux vomica overcome spasm, and give the patient a better night's rest than anything else that has ever been tried in the way of an anti-spasmodic or sedative." This last is a significant sentence. The fact that irritability of the nervous centres is the precursor of exhaustion is one that is well and generally recognized. The centres of respiration becoming exhausted, are abnormally irritable; the stimulant and tonic effects of strychnine upon them restores them to a comparatively normal state, and so sleep is undisturbed by irregular nervous action. Sedatives given under such circumstances would but further enfeeble these overtaxed centres, and so do much harm. The difficulty, of course, is to discriminate exactly the case for the stimulant tonic from that where a depressant sedative is indicated. In time, as our views on the subject become more orderly, and we progress from the present chaotic condition, this may, and almost certainly will, become more feasible and practicable. At any rate, these observations of Dr. Thorowgood stand in a very suggestive relationship to the conclusions just drawn from the results of experimental inquiry.

CHAPTER III.

THE RHYTHMICALLY DISCHARGING CENTRES; AND THE EFFECTS OF DRUGS THEREUPON.

The influence of the nervous system upon the different portions of the body, as muscular movement, secretion, etc., is, according to Hermann, as yet unknown, except in so far as we can regard the subject from a merely mechanical point of view. So regarded the nervous system is a "liberating force," *i. e.*, a force which leads to a conversion of a certain amount of potential into kinetic energy. He says further: "An infinitely small liberating force may liberate large quantities of kinetic energy, and it is exceedingly probable that even the liberating forces of the nervous system, if measured as forces, would be very small in amount, and consequently that the chemical changes necessary to their evolution, as to that of all the other forces of the organism, are of small magnitude." In consequence of the small amount of chemical change involved in the decomposition of the nerve-cells by which this liberating force is evolved, little as yet is known about the how of this action. That some chem-

ical change is essential is easily comprehensible. Blood containing oxygen is absolutely necessary to this chemical change, but the matter is somewhat complex, as we shall shortly see.

The nervous centres with which the present inquiry is engaged are those motor centres which govern the circulation and the respiration, and which discharge, or explode rhythmically, and send out efferent impulses which set up the requisite muscular actions. These centres exist for the circulation essentially in the ganglia of the heart, though in intimate connection with other parts, especially the vaso-motor centre in the medulla oblongata. For the respiration, as we shall shortly see, in the medulla solely; from which the efferent impulses requisite for setting the muscular mechanism of the respiration into action, are discharged. These two sets of centres are different from other motor centres in that they act rhythmically at brief intervals; the one, speaking broadly, discharging some seventy times per minute, the other about eighteen times per minute. The action of these centres rests essentially upon changes wrought in them by the blood supplying them; but their rate is affected by extrinsic forces which influence them through the nerves in connection with them. But these extrinsic forces are not an essential factor; it is necessary to be clear about this. The basis of action is the decomposition of the cells of these centres set up by the blood; for if

the blood to these centres be cut off, they cease to act. Wundt puts the matter thus: "Slight excitations generally vanish in the central substance of the cell, while stronger excitations set free its latent force. The excitations of the blood-current impinging on the periphery of the cells must accumulate until they reach a given strength, sufficient to liberate the force of the cell, which is thence transmitted to its central region, and thence to its motor nerve. After this discharge of force, equilibrium is restored, and the process begins all over again. Nerve centres submitted exclusively to the excitation of the blood act automatically and rhythmically. This rhythm is interrupted or rendered irregular when the influence of other nerve centres inhibits the discharge of accumulated force." Such then is the action, so far as at present we can tell, of the rhythmically discharging centres with which we are at present engaged.

The respiration will be gone into at some length later on; the cardiac ganglia will at present engage the attention. The action of the heart depends upon a series of ganglionic cells, connected by nerve fibres, which are lodged in the muscular structure of the heart, especially along the septum betwixt the auricles, and at the junction of these auricles and ventricles. When the heart is removed from the body, or separated from all the nerves supplied to it, it still beats for some time; in cold-blooded animals for days, in warm-

blooded animals so long as a supply of oxygenized blood is provided. The different nerve fibres, and especially those of the vagus, in connection with these cardiac ganglia but cause modification in the action of those automatically discharging centres, which are the cause of the rhythmic muscular contractions of the heart. The vagi nerves have however a potent influence over the discharges of the cardiac ganglia, and retard the rhythmic discharges. This is called an inhibitory action, and if these vagi nerves be irritated the heart's beats are slowed, and when the irritation is strong enough the heart is brought to a standstill in diastole. There are, however, accelerating fibres in the vagi which spring from the medulla oblongata, and which transmit impulses which accelerate the heart's action. Thus in emotion of certain kinds the heart's action is notably quickened, as is the case of the "blush," where at the same time the vaso-motor centre is implicated, and dilatation of the peripheral blood-vessels is induced.

Such are then the rhythmically discharging centres of the circulation. They are unique, but their action is not essentially different from the ganglia in connection with the intestines or the bladder. It is a difference of degree rather than of kind. We may now proceed to consider the action of drugs upon these cardiac centres, when we shall find several agents which possess a decided influence over them, viz., digitalis, aconite, and belladonna.

CHAPTER IV.

ACTION OF DRUGS UPON THE CIRCULATION.

DIGITALIS.

Some experiments illustrating the action of digitalis upon the heart were performed by me in 1870, and formed the counter-part to the clinical observations on which were founded the conclusions arrived at in my essay on Digitalis. The experiments were only of an elementary character, and performed on birds, fishes, and frogs. No calculation was made of the amount of the drug administered in each experiment. The part of the experiments interesting at present, is that where I elicited the antagonistic action of digitalis and aconite. Having compared the actions of these two drugs, and finding that digitalis brought the heart to a standstill in firm contraction, while aconite arrested it in full dilatation; the idea of testing their antagonistic action suggested itself. So aconite was given to frogs with their hearts contracted by digitalis; and in others digitalis where the heart was paralyzed by aconite. The aconite did not exercise a very marked effect upon the hearts contracted by digitalis, but the other experi-

ment was very successful. "When all action had apparently ceased, the first effect of the administration of digitalis was to produce an imperfect contraction at long intervals; then the intervals became shorter, and the contractions more complete, some irregularity, both as to time and amount of contraction, being observed. Slowly and gradually, however, the distended ventricle recovered itself under the action of digitalis, the contractions being more rythmical and perfect, and the distension less and less pronounced, until a return to normal contraction and distension was brought about. If the administration of digitalis were then continued the same appearances were brought about as when no aconite has been previously given." Attention was drawn to these experiments by the fact that shortly after this Dr. Dobie, of Keighley, administered digitalis to a man dying of aconite poisoning with the result that the man recovered. To this case reference will be made in a later section of the essay. This line of experiment was followed out by Boehm, who found that muscaria, delphinia, and aconitia would restore cardiac action in the frog when arrested by digitalis poisoning. More recently further experiments as to the antagonism of digitalis and aconite in warm-blooded animals have been made, of which an account has been given above.

The effects of the experiments of myself and of Boehm went to corroborate the views of Traube and others, that digitalis was not a cardiac sedative in the

ordinary sense of that word. That is, it did not calm the heart's action by depressing the activity of its nervous centres. The old view was that digitalis lowered or moderated the heart's action, and it was called "the opium of the heart." But this view has given way to another, viz., that digitalis excites more perfect contraction of the cardiac ventricles. Traube had observed that the effect of digitalis was to increase the blood-pressure in the arteries. Then Malan and myself observed that it contracted the arterioles, while Fuller and Handfield Jones had experimentally ascertained that in animals poisoned by digitalis the heart was firmly contracted, and so contrasted with the state produced by aconite and chloroform. Eulenberg and Ehrenhaus had noted that a frog's heart, when removed from the body and its apex dipped in a solution of digitalis, was so brought to a standstill in systole.

Consequently the position which digitalis now holds is that of a cardiac tonic, *i. e.*, it increases the energy of the ventricular contractions. It tends, as Niemeyer puts it, to fill the arteries by emptying the veins. Consequently digitalis is now administered in cases of cardiac failure, where the heart is inadequate to the duty of propelling the blood forward in sufficient quantity. It does not matter what the state of the heart is so much, whether hypertrophied or dilated; the real question is this: Is the heart equal to its work? Even with considerable hypertrophy the heart may still be

unequal to its functional duty, and the hypertrophy may be insufficient. Under these circumstances the administration of digitalis is indicated, but in lesser doses than in dilatation. The dose must be proportioned to the natural efforts at compensation. If a fairly good compensatory hypertrophy is being naturally instituted, then small doses of the drug are alone required: if the ventricular chamber is prominently dilating, then large doses are absolutely necessary. Under the latter circumstances doses of digitalis are well borne and do great good, which would produce very serious symptoms if given where the heart is considerably hypertrophied. The theory propounded by me is this: Digitalis excites more perfect ventricular contraction, the arteries are better filled with blood, and consequently the heart itself is better nourished; while the brief diastolic sleep is lengthened. Betwixt the longer rest and the improved nutrition the heart is enabled to grow and to increase in power. This view is borne out by the observations of other authorities. Traube's observations as to the increased blood-pressure in the arteries produced by digitalis have been corroborated by Lauder Brunton and others; and it is no longer in dispute that the arterial tension is increased by this drug, except in distinct poisoning when it falls. Thus Balthazar Foster has shown that the slowing of the pulse by digitalis is achieved by lengthening the diastole, not by any effect upon the length

of time of the systole. Thus the above view of an improved nutrition and a longer rest is seen to be sound. As long as the blood-pressure in the arteries can be maintained, all is well. The aortic recoil fills the coronary vessels, and the heart is sufficiently supplied with blood, and so its tissue integrity is maintained. But when the blood-supply to the heart is unequal to its proper tissue repair, then molecular decay is inaugurated. Mauriac has pointed out how soon the massive hypertrophy of aortic regurgitation fails early, from the blood-supply to the coronary vessels becoming impaired from the insufficiency of the aortic valves. Normally these valves arrest the backward flow of the blood on the aortic recoil, and the coronary vessels in the sinuses of Valsalva are well filled with blood: but as the valves become more and more incompetent, the flow into the coronary vessels is diminished, and the heart's nutrition is impaired. Consequently the prognosis of a case of aortic regurgitation is widely different from that in aortic stenosis, or in mitral disease; because in these latter cases the blood-supply to the heart can be pretty well maintained, while in aortic insufficiency it soon fails. These conclusions are confirmed by the clinical observations of Balthazar Foster, that the subsequent history of a case of traumatic rupture of the aortic valves is profoundly modified by the fact which valve is ruptured. If it be that cusp behind which there is no coronary artery, the case will last

comparatively a long time. But if the torn cusp have an artery behind it, then the nutrition of the heart is soon affected, and the case runs its course in much less time.

The use of digitalis in practice is, as nearly as is yet arrived at, as follows. (In the Competitive Essay digitalis was very briefly dismissed, as any lengthy consideration might have revealed the individuality of the writer. Now there exists no objection to such consideration. Further, my Essay on Digitalis[1] is now out of print, and is not likely to be republished; and the present offers an opportunity of making the views there put forward available for those who might desire to consult the original essay, and are no longer able to do so.) When the heart, from any cause, ceases to propel the blood forward into the arteries, the system suffers from the want of arterial blood. The arteries are insufficiently filled, while the veins are surcharged with blood, and a whole series of pathological sequences follow from the venous fulness; among therest a development of connective tissue in the viscera, as the lungs, the brain, the liver, spleen, and kidneys; there is fulness of the venous radicles of the stomach, and therewith impaired digestion and a constant feeling of "fulness" as if the stomach were distended

[1] *Digitalis: its Mode of Action and its Use*, to which was awarded the Hastings Gold Medal of the British Medical Association for 1870.

with a liberal meal, when in reality it is empty; there is albuminuria from congestion of the renal veins, and not rarely serous effusions from the intestinal venules, forming diarrhœa. The organs connected with the valveless portal circulation especially feel any venous congestion from failure in the central organ of the circulation. The tissues, including the muscular structure of the heart itself, are suffering from want of a sufficiency of arterial blood charged with nutritive material. When digitalis is administered, the ventricular contractions become more complete, and the arteries are better filled, and consequently the veins more thoroughly emptied. When there is pronounced dilatation of the heart, and a little blood is pumped out only at each systole, and the heart is soon full to distension, it quickly contracts with an inefficient systole, the pulse being rapid, feeble, and compressible. Thus it is that digitalis so promptly affects the pulse-rate. By its effects upon the cardiac ganglia it causes a slower but more energetic discharge of force, and with it a more powerful muscular contraction. The systole is more complete, the chamber is more efficiently emptied, and consequently is not so soon refilled, so that the requirements of the ventricle in diastole correspond to the slower rhythmic discharges, and a slower pulse-rate is established; while the pulse is firmer and less compressible, the arteries being better filled with blood. At times digitalis will notably lower the pulse-rate

under other circumstances than those just mentioned, illustrating its effects upon the discharging cardiac ganglia. When the pulse-rate falls very markedly under its use, as when it falls below 50, it would be well to substitute belladonna, squill strychnia, or casca for it.

"The series of altered actions consequent upon increased ventricular contraction run in the following order or sequences: and it may be desirable for the sake of lucidity to arrange them in a series of propositions, each depending on the one before, like a logical syllogism. The effects of increased contraction, then, are—

1, Increased arterial distension and tension, which give relief to the systemic symptoms, and further causes,

2, Increased arterial recoil. This is the propelling power for the coronary arteries; and thus increased arterial recoil means,

3, Increased or improved coronary circulation; and this, in its turn, produces,

4, Increased nutrition of the heart, which results in

5, Compensatory hypertrophy.

"Not only is improved nutrition of the tissues of the heart thus secured, but the brief diastolic sleep is lengthened: and betwixt a longer sleep and an improved nutrition the heart structure is repaired efficiently, and recovers its tone more or less completely, according to the nature of the case."

Consequently, as said before, in fairly good hypertrophy, digitalis is either not indicated at all, or if so, only in small doses. As digitalis not only acts powerfully on the heart itself, but also produces contraction of the peripheral arterioles, and so raises the blood-pressure in the arteries, it should not be given in hypertrophy in large doses; especially where the arteries are atheromatous, as it greatly increases the risk of apoplexy from rupture of an encephalic artery. Such an accident has occurred from the use of digitalis, even when the hypertrophy was commencing to fail in incipient fatty degeneration.

In dilatation however its use may be free, not only without danger, but with positive advantage. "In dilatation, where the system is confessedly unequal to the establishment of compensatory hypertrophy, the use of a drug whose action is to throw the ventricle into a state of tonic contraction is readily understood as being of the greatest service: and this also explains how its use in large and continued doses is not only not productive of symptoms of poisoning, *i. e.*, of ventricular spasms, which was once imagined to be due to an accumulation of the drug in the system in some mysterious inexplicable manner,[1]—but is even necessary to

[1] There is no accumulative action connected with digitalis any more than with belladonna, strychnine, arsenic, or mercury. If these agents be taken into the system in doses in excess of the eliminative powers, they "accumulate," and produce toxic symptoms. But they do not "lie in wait" to work mischief.

the continuance of life. Without it or some similarly acting drug, dilatation must become only more and more extensive, and hand-in-hand with that extension must be an increasing inability on the part of the heart to recover itself; hence still more enfeebled circulation, blood stasis and its consequences, until the widening vicious circle ends in somatic death." It may indeed be questioned if any risk can be incurred by the free administration of digitalis in cardiac dilatation until the dilatation is notably reduced. In the case of a girl, M. C., *æt.* 19, with aortic regurgitation and an enormous dilatation of the left ventricle, whom I sent into St. Mary's Hospital under Dr. Broadbent, the use of digitalis in the hospital was followed by a reduction of the dilated ventricle of a very pronounced character. After which severe palpitation came on, and ceased when the digitalis was withdrawn. On coming out of the hospital and again moving about, it became necessary to resume the digitalis, which she continues in small doses still, now two years since she was in St. Mary's. In the case of a huge man, a patient at Victoria Park Hospital, with an enormously dilated heart, without any valvular mischief, it has become needful to exhibit digitalis in unusually large doses (Tinct. Digitalis ♏ xx. Tinct. Nucis. Vom : ♏ xv. Ter in die) to enable him to work—for rest he will not. Commonly this reduction of a dilated heart—and with it the size of the mitral ostium—will enable par

tially injured mitral vela to close the ostium completely on the ventricular systole; that is, these valves are rendered once more functionally competent. At other times the reduction of a widely dilated ventricle, with corresponding augmentation of its power, will develop a mitral systolic murmur previously inaudible. In cardiac dilatation digitalis may be freely exhibited, and if the practitioner feel somewhat afraid of such use of it, he may combine it with strychnine and carbonate of ammonia—an addition which ought to relieve his mind of every apprehension.

In valvular disease of the heart digitalis may be resorted to with great advantage; but there are points in each form of valvular lesion to be attended to which are important enough to make mention of them desirable. To take them in order is probably the best plan.

Aortic Obstruction.—Here there is a distinct obstacle to be overcome, namely, a narrowing of the aortic orifice. This is usually achieved by the natural powers alone, and aortic obstruction commonly does not come under the notice of the physician unless the patient has been pulled down by some intercurrent condition or malady. In elderly persons, however, it presents itself primarily with certain objective and subjective phenomena. Here a new balance can only be effectually struck by an increase in the driving power, so that the normal amount of blood may be driven through a narrowed orifice in the normal time. According to

the view that digitalis slows, or retards the systole, and so permits the blood in the ventricle to be completely passed through the narrowed orifice, the wants of the system would be no more perfectly met than before. But against this view are the facts that in unaided hypertrophic compensation in aortic stenosis there is no such elongation of the systole; and that Balthazar Foster has shown that digitalis does not slow the systole, but lengthens the diastole. In aortic stenosis digitalis is indicated in small or medium doses according as the hypertrophied ventricle can, or can not, quite successfully meet the obstruction offered. If the ventricle cannot completely empty itself, and blood is accumulating in the left ventricle, *i. e.*, a condition of dilatation is being established, then digitalis is clearly indicated. When there is no dilatation, and the compensation is sufficient, digitalis is not required.

Aortic Regurgitation.—Here a complex problem is presented to us, for the hypertrophy here, often enormous, is to antagonize the increased internal pressure upon the heart-walls during diastole; not to overcome any obstruction offered. There being a decided increase in the distending force, there is dilatation in spite of the massive hypertrophic growth. This enlargement of the left ventricle, in capaciousness as well as in power, causes at each systole a largely increased mass of blood to be suddenly thrown into the arteries

on each ventricular systole, and that, too, with abnormal force. Consequently the arteries are over-distended and become ruined rapidly by atheroma. The hypertrophy which limits dilatation in its turn does harm, and some writers call this condition "over-compensation." Here, and at this stage digitalis, which would lengthen the diastole and increase the vigor of the ventricular systole, is contra-indicated. A drug of opposite action, which would shorten the diastole and diminish the vigor of the systolic contractions, would be desirable. But in the later stages, when the hypertrophy is failing and the heart-walls, undergoing decay by fatty degeneration, are once more yielding to the distending force, then digitalis is indicated to prolong life. The danger of sudden death by over-distension of the failing ventricle in diastole is great in the later stages of aortic regurgitation, and here digitalis is useful: but each case requires its own management and not rules of thumb.

Mitral Disease.—In the consideration of the use of digitalis in mitral disease it will serve no good practical end to separate stenosis and regurgitation. In the one case the blood is obstructed by a narrow orifice, in the other it is damned up by a backward flowing current. The results are the same. The auricle is dilated, the flow of blood in the pulmonic circulation impeded, the pulmonary artery and its branches are dilated and thickened; the obstruction in the pulmonic circulation

leads to enlargement in the right ventricle, hypertrophy, with more or less dilatation. As long as the right ventricle can contract efficiently upon its contents the blood is driven forward successfully, and the increased obstruction met. When this capacity of the right ventricle is naturally established, all is well; but when the system unaided is unequal to such compensation, or the compensatory hypertrophy is failing, then digitalis is of the greatest service. There is no difference of opinion in the profession about the utility of digitalis in mitral disease. By its effects in procuring more perfect ventricular contraction it exercises the most beneficial action upon the failing right ventricle. Where there is accompanying bronchorrhœa digitalis is not contra-indicated, but the reverse. The bronchial flow is not the measure of the blood-pressure in the pulmonary circulation, but of the stagnation in the bronchial veins, a part of the general venous congestion; and the administration of digitalis lessens the bronchial flux, while it raises the blood-pressure in the pulmonary vessels.

Right-Side Dilatation.—Digitalis is of the greatest service in dilatation and failing power in the chambers of the right heart, whether from mitral disease or chronic changes in the lungs, as cirrhosis of them, or where there is chronic bronchitis or emphysema, or chronic pleuritic effusion, or other cause of obstruction to the blood-flow in the pulmonic circulation. In such

cases it is well to bear in mind the co-existent embarrassment of the respiratory centres and to combine with digitalis ammonia, nux vomica, or belladonna.

Tricuspid Regurgitation.—When the tricuspid valve has become insufficient, then our efforts carry with them little success, because we have no muscular chamber behind the lesion to be acted upon; the muscular fibre in the venæ cavæ being but small and powerless. Still it may be tried in combination with brisk purgation to relieve the portal circulation.

In *temporary cardiac conditions* of asthenia digitalis is useful, as in cardiac dyspnœa, with over-distension of the right ventricle. If the over-distension is threatening paralysis in diastole, it may be well to relieve it by venesection, giving ammonia and digitalis at the same time. When the right ventricle has been overstrained by long-continued efforts, as in long runs, diving, etc., digitalis is useful. The right ventricle is apt to become overstrained where the breath is long held, or the circulation in the lungs impeded; and the person is less equal to an effort, instead of more equal; this, in sporting phrase, is termed to "train off," in contradistinction to continued improvement and capacity, which is termed "training on." It is worth while trying the effects of digitalis in horses whose wind has been impaired by long severe effort (over-distension of the right heart), or even in broken-windedness from emphysema. Of course in the latter

case only some improvement can be looked for; but in over-distension of the right heart even more seems potentially attainable. Of course stimulants to the respiratory centres at the same time are indicated.

In *Shock*, digitalis with ammonia and nux vomica, is likely to be of much service, and it has already been so used with good effects.

Palpitation.—In palpitation due to exhaustion, or to muscular failure, digitalis is very useful. Here palpitation is the active expression of incapacity in the heart. It is over-taxation, not over-action, with which palpitation is here associated. It may occur with a heart dilated, hypertrophied, or normal, but it indicates want of power. Here digitalis and iron, with rest, are clearly indicated. In the palpitation of gout, and in those forms wherever it is truly neurosal, or of reflex origin, digitalis does little good.

Fatty Degeneration of the Heart.—Here digitalis can only be of use for its action (through the cardiac ganglia) upon the muscular fibres remaining sound. Where the heart is failing obviously, and losing its rhythm, digitalis will be of service. There are two points to be considered here though, and they are both related to the question of internal pressure. Firstly, if the degeneration be unequal throughout the heart, to increase the blood-pressure in systole is to increase the pressure on weakened spots, and so to cause cardiac aneurism, or even rupture—or at least to run the risk

of doing so. Next, fatty degeneration of the heart is usually associated with advanced atheroma of the vessels, and so is "a preservative lesion," and where so associated, to increase the vigor of the heart's contractions on the one hand, and tighten the arterioles on the other, would lead to an increase of the internal pressure within the arteries, and so to markedly increase the danger of rupturing them. Still here it is usually desirable to administer digitalis, in spite of these theoretical objections.

In cases of anæmia with unfilled vessels it will usually be found advantageous to give digitalis. By increasing the activity of the heart and contracting the arterioles it tightens the vascular walls upon their fluid contents, and so raises the blood-pressure in the arteries. Consequently it is of great service in cerebral anæmia, along with tonics and hæmatics.

In considering the action of digitalis it must be borne in mind that it not only acts upon the cardiac ganglia, and so excites more perfect contraction of the heart itself, but that it acts also on the vaso-motor centre, and produces contraction of the peripheral arterioles. If it did not possess this second action digitalis would be of little therapeutic use, for as fast as the ventricle threw blood into the arteries it would escape by the open arterioles. By obstructing the out-flow, as well as increasing the blood-flow into the arteries, digitalis raises the blood-pressure in the

arteries. It fills the arteries, and in doing so empties the veins. It thus relieves the symptoms consequent upon arterial anæmia. The flow of urine is ordinarily the measure of the arterial fulness. As Traube pointed out, the bulk of urine is the measure of the blood-pressure on the renal glomeruli; and this usually is in direct proportion to the general blood-pressure. Consequently many persons who have not carefully studied the mode of action of digitalis say: "It always does good when the bulk of urine is increased;" or: "It always does good when its diuretic action is established." Quite true! But this diuretic action is really the evidence of its effect upon the circulation. When it increases the bulk of urine digitalis is producing its effect upon the circulation.

There is just one more point to be noted in the action of digitalis, and it is this: If digitalis contracts the terminal arterioles, it must cause further obstruction to an already enfeebled heart, it may be argued. This is quite true. But when the heart is distended its sensory nerve throws the vaso-inhibitory nerves into action, and so dilates the peripheral arterioles. Digitalis restores them to their normal calibre, while it acts directly upon the heart, increasing the vigor of its contractions. Any risk of increasing the obstruction offered to the ventricular systole, so as to embarrass the heart, must be regarded as hypothetical

rather than practical, like the dangers of its use in fatty degeneration.

From its effects upon the heart and arterioles, digitalis is used to lower the body-temperature in certain pyretic conditions where the arterial tension is low. According to Ackermann and Heidenhain the temperature and the blood-pressure vary inversely; when the blood-pressure is raised, the temperature falls; when the arterial tension falls, the temperature rises. Digitalis has been found very useful in pyretic states where the heart is likely to fail, as in typhoid pneumonia, relapsing fever, etc. The modern use of digitalis has been reached as much by the aid of experiment as clinical observation. Indeed clinical observation, as the history of the drug shows, absolutely needed the aid of experimentation to direct it aright.

The history of digitalis as a therapeutic agent is most instructive. The views taken of its action represent the pathological opinions of the time. When hypertrophy was a wanton and useless, indeed dangerous overgrowth, digitalis was a sedative, because it quieted the tumultuous action of the heart. Now, when we recognize that hypertrophy is a useful compensatory growth, we discover that digitalis is a stimulant to cardiac action, and quiets the heart by enabling it to contract more efficiently, and therefore more steadily. The whole question of acting upon the heart in the way of increasing its power is quite a recent

one. It is now acknowledged generally that we can stimulate the heart to contract more efficiently by means of digitalis, belladonna, and strychnia. It will be seen that not only can we do this, but that there are excellent grounds for holding the view that now we are in a position to systematically and designedly excite more perfect respiratory action when it is desirable to do so. We possess agents which will stimulate the nervous centres of respiration when becoming embarrassed, so that they will once more respond to the natural stimuli to action. It will be seen that the agents which possess this power are also those which act upon the circulation, and some difficulty will arise from this combined action; nevertheless it will be possible to demonstrate that there exist drugs by which the respiratory centres can be stimulated and excited into more perfect action when failing. These agents are ammonia, belladonna, and strychnia, which are not expectorants in the sense that they exercise any influence over the bronchial secretion, but that they affect the nervous centres of the respiratory organs, and excite more perfect respiratory action. We can maintain the respiration when failing in acute bronchitis as certainly as we can excite cardiac activity in syncope, or when the heart is failing in acute disease. Probably any action upon one system involves action on the other, but that will not constitute an insuperable difficulty in the inquiry.

Digitalis produces its effects upon the heart, not by acting upon the muscular structures, but through the nervous centres which excite muscular action. It is a direct stimulant to these centres, in that it increases the energy of their rhythmic discharges. It causes these discharges to become more energetic, and under certain circumstances much slower. Nerve centres when becoming exhausted usually become irritable, that is they act rapidly and with little energy. Under these circumstances a direct stimulant to them lowers the number of the rhythmic discharges, but increases them in power. Digitalis and belladonna have a very powerful action upon these cardiac centres, and so has strychnia; while aconite depresses them, as also do the well-known neurotic sedatives opium, chloral, and bromide of potassium. When we wish to stimulate the energy of these cardiac motor centres we give digitalis, belladonna, or strychnia. Thus in cases of failure of the heart these agents are indicated and do good. In the palpitation of muscular failure they are of service; but in the palpitation of nervous excitement, where the cardiac centres are acting too energetically, they are contra-indicated, and sedatives should be used. We are so accustomed to think and speak of the heart from its muscular side only, that we are apt to overlook in thought, and certainly omit in speech, the intimate connection existing betwixt the heart and its nervous centres. Yet all these agents

act upon the muscular walls through the nerve ganglia which preside over them.

BELLADONNA.

Belladonna acts powerfully upon the heart, and has long been a favorite agent in conditions of palpitation of a chronic character. Dr. John Harley states that it causes a rise of blood-pressure in the arteries, and that therefore it is the drug *par excellence* to be used as a diuretic agent when the arterial pressure is low; Dr. Graves commended its use in typhus fever in the advanced stages; and many writers have extolled its utility in conditions of circulatory debility. From what we shall shortly see of its action upon the respiratory centre it is an agent undoubtedly called for when the circulation and respiration are failing. It has been resorted to very successfully in the treatment of collapse by Reinhard Weber, M. D. (*Philadelphia Medical Times*, February 2d, 1878.)

ACONITE.

The action of aconite upon the heart is a very powerful and very decided one. A moderate toxic dose produces at first a reduction in the number of heart pulsations, then an increase with evident loss of power, and finally irregular systolic movements with very long intervening pauses ending in diastolic arrest

(Achscharumow, Böhm, and Wartmann). According to these latter authorities in aconite poisoning the force of each individual beat is lessened; and after death the cardiac muscle fails entirely to respond to galvanic irritation—its contractility is lost.

Aconite has been used of late very largely, for the purpose of quieting the circulation when excited, especially in febrile conditions. Sidney Ringer has done much to bring this agent into notice for the alleviation of pyretic states, especially in children. It lowers the action of the heart, and also of the respiration, and so lessens the chemical interchanges going on; at the same time that it dilates the cutaneous vessels and throws the sudoriparous glands into action, and so increases heat loss. Its effects are very distinct, and for children it really is an excellent measure. In my experiments I found the younger rabbits to require a larger quantity of aconite to the pound weight to produce a lethal effect than in older rabbits. (One-three hundredth ($\frac{1}{300}$) of a grain of aconitine was a lethal dose for a 3 lb. rabbit; while for a rabbit weighing $1\frac{1}{2}$ lb. not a six-hundredth ($\frac{1}{600}$), but a four-hundredth ($\frac{1}{400}$) of a grain was the lethal dose.) The same holds good in man, and Dr. Farquharson recommends great caution in its use in the aged, and extols its utility in children. Aconitine, then, can be usefully employed when we desire to lower the heart's action when excited. It affects the muscular contractions

through the nervous ganglia, whose discharging intensity it lessens.

These three drugs just enumerated exercise an influence over the circulation and respiration which is very marked, and out of all proportion to their action upon other parts of the nervous system. Other agents, as strychnia, as an excitant, and opium, chloral, bromide of potassium, as sedatives, exercise the same action upon the cardiac centres that they do upon the nervous system generally, and may be resorted to with advantage in many abnormal conditions.

So much for the action of drugs upon the circulation.

CHAPTER V.

THE RESPIRATION.

It may now be well to consider the subject of the respiration, the means by which it is conducted, the circumstances which influence it, and the action upon it of certain medicinal agents, as ascertained by recent experimentation and observation. It is considerably more difficult to present a brief, lucid, and yet withal fairly accurate sketch of the nervous mechanism of the respiration than it is of that of the circulation. In each there are rhythmically discharging centres—motor centres which discharge or explode at recurrent intervals. But in addition to these there are nerve-fibres in connection with them which may cause them to discharge more quickly, called accelerator nerves; and others which retard the discharges, called the inhibitory, or restraining nerves. The respiration is, too, to a much greater extent under the control of the will than is the action of the heart. Voluntary effort may slow the respiration pronouncedly, but it cannot arrest it; the necessity to breathe becomes too im-

perious for any exercise of the will. Both are largely influenced by the emotions.

Such are the arrangements common to both the respiration and the circulation. The peculiarities of the respiration may now be reviewed. Breathing is an involuntary act, which persists during unconsciousness. It depends upon a centre in the medulla, and continues after all parts of the brain above the medulla are removed. On the other hand, if the cord be divided just below the medulla all the thoracic movements necessarily cease; but that the centre is still in action is evidenced by the fact that the respiratory movements of the nostrils and glottis still continue. The respiratory centre, the *nœud vital* of Flourens, is placed in the medulla, below the vaso-motor centre; and if this *nœud vital* be excised, though all other portions of the nervous system be left untouched, the respiration stops. Respiration is maintained by the action of the blood upon this centre. It is in communication with the lungs by means of the vagi, and is probably more or less influenced by certain conditions of the lungs, for when the vagi are cut the respiration is modified, it becomes deeper and more prolonged; it is fuller and more complete. What it loses in rapidity it gains in depth. The vagi contain both accelerating and inhibitory fibres, the accelerating fibres preponderating. Consequently section of the vagi slows the respiration; but to compensate for this the inspiratory

act is deeper and fuller. It is in this respiratory centre that the action of breathing takes its origin: not in the peripheral terminations of the vagi in the lungs. In ordinary respiration certain muscles only are set in action, but under other circumstances the energy of the discharge is felt in the accessory muscles, by which a more vigorous act is determined; and in dyspnœa nearly every muscle of the body is thrown into action.

The next point to be considered is the effect of the blood upon this respiratory centre—this rhythmically discharging motor-centre—whose action is so essential to life. We have seen that the removal of all the brain above the medulla leaves the breathing unaffected; section of the cord below leaves the centre unaffected, the respiratory action of the nostrils continuing as before: but if this *nœud vital* alone of all the cerebro-spinal system be excised, the respiration ceases entirely. The effect of the blood passing through this centre upon it is to excite the discharge which causes the respiratory movements. The more venous the blood, the greater the activity of this respiratory centre. The effect of venous blood is to augment the natural explosive decomposition of the nerve-cells of the respiratory centre; it increases the respiratory impulses, and quickens their rhythm. The effect of defective arterialization causes more rapid as well as deeper breathing; more perfect and extensive respiration is set up until properly arterialized blood is pro-

cured. The absence of oxygen rather than the presence of carbonic acid is the exciting cause of this more energetic respiration. Thus if the blood-supply to the medulla be cut off by ligature of the arteries of the neck, dyspnœa is produced. On the other hand a rabbit in which artificial respiration has been vigorously carried on ceases to breathe for some time until the blood becomes venous again. This condition of apnœa—true physiological apnœa—is induced because for a time the blood is so highly oxygenated that the respiratory discharge is delayed; it takes some time for the blood to become sufficiently venous to excite respiratory action. Such is the condition of true apnœa.

The opposite condition, dyspnœa, is the reverse of this. In dyspnœa more violent respiratory efforts are set up. The respiratory impulses overflow their ordinary routes until nearly every muscle of the body is thrown into contraction. The more venous the blood the more vehement the discharges, and the more extensive the respiratory act; but if the blood becomes too venous the respiratory centres cease to act. A little accession of oxygenized blood will, however, again set them in action. A certain, but small, amount of oxygen is necessary to the rhythmic discharges. In dyspnœa the expiration, as well as the inspiration, becomes more pronounced. The impulses generated by the presence of highly venous blood, or, more correctly, blood abnormally deficient in oxygen,

are more than ordinarily energetic, in order to induce respiratory movements powerful enough to oxygenize the blood. If they are sufficiently vigorous to attain this end the dyspnœa is relieved; if insufficient, the dyspnœa passes into asphyxia. The greater the necessity for respiration, the more energetic the explosive discharges generated, until either the condition is relieved or the efforts fail. In ordinary respiration a certain group of muscles are set in action; if the breathing is more difficult, a wider area of muscles is involved, viz., the accessory muscles of respiration; if the dyspnœa be urgent, the impulses generated by the respiratory centre are felt in every part of the muscular system. Thus the system is protected against asphyxia until the centres can no longer carry on the struggle, and fail. The breathing gradually becomes slower, the enfeeble respiratory centre takes some time to develop an expiratory explosion; but the impulse, when it is generated, is proportionately strong.

This review of the mechanism of normal respiration will enable the reader to grasp all the more readily the action of certain drugs upon this mechanism; and without such knowledge of the respiratory movements it is impossible to intelligently comprehend the effects of certain powerful toxic agents.[1] The respiratory

[1] This account of the respiration will be found in agreement with our most recent works on physiology, and especially the able work by Michael Forster, F.R.S.

centre is not merely a reflex centre; it is higher than that, it is automatic. Efferent impulses start *de novo* from the centre itself; the respiratory movements are not merely reflex. An explosive discharge is generated within the centre itself and sets up the respiratory movements. The more venous the blood, *i. e.*, the more deficient the blood is in oxygen (provided that it still contains some oxygen), the more frequent and more energetic are the movements set up. On the other hand, when the blood is super-oxygenated, apnœa is induced for a time, until the disappearance of the oxygen from the blood excites respiratory impulses. It seems probable that this explosive decomposition of the nerve-cells is due to the formation of some substance which has its activity diminished by the presence of oxygen in large quantities. When oxygen is present in excess the respiratory explosion or discharge is arrested; when oxygen is present in normal amount ordinary respiration is found; when oxygen is deficient, dyspnœa is induced—the respiratory explosion or discharges, are more frequent and more powerful, and extend over the whole muscular area. When oxygen is entirely absent they cease utterly.

Further than this in the present state of our knowledge we cannot go, but the above *résumé* is sufficient to throw a flood of light upon the action of certain drugs upon the respiration.

Thus Prof. Frazer found Calabar bean to have a

profound effect upon this centre, and that atropine counteracted its effects. Prof. Bennett and Oscar Liebreich found chloral and strychnia to have an antagonistic action to each other; while the writer found aconite to be effectually antagonized by atropine and strychnia.

We will now review the action of these different agents by the light of the above *résumé*. It will be seen that certain agents, as strychnia, chloral, and morphia, possess the same action over the respiratory centre that they exert over the nervous system generally; while aconite and atropine exert an influence chiefly upon the rythmically discharging centres (those of the circulation and respiration), and do not apparently affect the rest of the nervous system, that is to anything like the same extent, at least comparatively.

To take *aconite* first. When a rabbit is dying of aconite poisoning its respirations become slower and deeper, the movements are violent, and then convulsive, until the animal dies from exhaustion of its respiratory centres. If the dose be large the heart is found still to have been contracting strongly, and after death it is found in systole. If the dose be smaller, and the act of dying is more prolonged, then the heart fails too, and is found in diastole. It is found in aconite poisoning that the force of each individual beat is lessened; and that after death the heart fails to respond to galvanic irritation. Aconite acts most potently upon the circulation and respiration, over which the rhythmically

discharging centres preside. When a rabbit is dying of aconite poisoning the respiration becomes gasping and slow; and at every fifth respiration, or nearly so, there is a violent gasp, with a general struggle. Thus we see the phenomena of dyspnœa clearly produced, the breathing becomes more energetic, while slower, the muscular movement becomes general, and then the centre fails. If an antagonistic agent in sufficient dose be given the respiration becomes quickened, and as it grows quicker the extent of the muscular area involved is diminished until normal respiration is attained. Aconite acts very decidedly upon the respiratory centres; and this effect is not produced by any stimulation of the inhibitory nerves of the vagus, and so arresting the action of the discharging centre, but by the effects upon the centre itself (Böhm, and Wartmann, and Liégeois and Hottot); because previous section of the vagi did not influence the action of aconite upon the respiration. The writer fully agrees with the conclusion arrived at by H. C. Wood, "that aconite is a direct depressant and paralyzant of the respiratory centres."

Then as to *Calabar bean*. Prof. Frazer found the respirations and the pulse-beats to be distinctly lowered by Calabar bean until they became undistinguishable. After the administration of atropia both were notably quickened, indeed the normal rapidity was exceeded for a time after which they fell to their wonted rapidity. Calabar bean kills by paralyzing the rythmically dis-

charging centres of the circulation and respiration; and atropia saves life from toxic doses of this poison by its antagonizing and stimulant effects upon these exploding centres.

Then as to *chloral*. This agent depresses all nervous action when administered systemically, and possesses a potent influence upon nerve areas when applied locally (Dowse). The action upon the centres of the circulation and respiration differs not from its general action upon the nervous system, unless it be in degree. "It kills by paralyzing the centres of the circulation and respiration, especially the latter. In toxic doses it brings the respiration to a standstill, the heart being found flaccid in diastole. In full doses chloral lessens the number of the respirations per minute, causing them to become slow and full; in toxic doses this becomes more marked, until finally the rhythm is very much affected and the respiration grows very irregular, and sometimes very rapid and shallow, or even slow and shallow, until it finally ceases. As these phenomena occur equally after section of the vagi the influence of chloral must be exerted upon the respiratory centre at the base of the brain. "In fatal doses it causes death by arresting, through paralysis of the nerve-centres, first respiration, and finally the heart in diastole" (H. C. Wood). Again in chloral we see the respiration fail, but not exactly the same as in aconite poisoning. The generally paralyzing

effects of chloral prevent those convulsive and extensive respiratory movements found in aconite poisoning.

Then as to *opium*. Opium and its derivative, morphia, act upon all nerve centres; but they act especially on the respiration. "To maintain respiration is the ultimate object of all the measures which are commonly undertaken for the purpose of arousing the system in opium-poisoning. Unconsciousness in itself is of no moment, but as it deepens, the sensibility of the respiratory centres grows less, and consequently the involuntary breathing is less rapidly and perfectly performed. When other measures fail artificial respiration should be resorted to and steadily maintained until all cardiac action has ceased or recovery taken place" (H. C. Wood). Here again we find the circulation waiting upon the respiration, which is the first to fail. "Death occurs from opium, in the great majority of cases, by failure of the respiration; and that such failure is due to a direct action of the poison upon the respiratory centres in the medulla is proven by the fact that morphia affects the breathing of dogs and rabbits whose pneumogastrics have been cut as much as it does those whose nerves are entire (Gscheidlen)."

Thus we see there are two classes of agents which paralyze the respiratory centres: 1, those which act upon the nervous system generally and the rhythmically-discharging centres especially; and 2, those

agents which act chiefly upon the latter. The first division comprises chloral and opium, the latter aconite and Calabar bean.

We may next profitably examine the action of agents which directly stimulate the respiratory centres. They also influence the other rhythmically acting centres—those of the heart. To take *strychnia* first. The action of strychnia upon the respiration has not yet been specially studied, as has its action upon its circulation, except by Prokop Rokitanski. It has to be read mainly by the antagonism it exercises towards certain other toxic agents. Bennett and Liebreich found it to exercise an influence over lethal doses of chloral, but not to the extent that chloral influenced strychnia poisoning, though still enough to demonstrate the antagonism. I found it to exercise a very distinct and pronounced influence over lethal doses of aconite. In my opinion the rabbits which died with the symptoms of strychnia poisoning in my experiments died of expiratory spasm. It was as if the respiratory centre was thrown into a state of tetanic spasm, and inspiration was no longer possible: the same phenomenon as occurs when the central end of a cut vagus nerve is severely irritated. That strychnia does exercise such an effect upon the respiratory centres and cause expiratory spasm as well as active inspiratory efforts is evidenced by experiments. Leube and Rosenthal found that artificial respiration prolongs and even saves life,

according to the amount of strychnia poisoning injected. And Schiff corroborates this, for he found that animals in which forcible artificial respiration was maintained survived doses much larger than those ordinarily fatal. The artificial respiration was performed by inserting a canula into the trachea and filling the lungs by force (H. C. Wood). It is clear that the action of strychnia is to excite or stimulate the respiratory centre ; but that, in lethal doses it acts most pronouncedly upon the expiratory portion of the respiratory act.

Lastly, *atropia*. The action of belladonna upon the respiration is a very important one. Like aconite, it acts specially on the rhythmically discharging centres, which rule over the respiration and the circulation. It has, however, a more marked action upon other parts of the cerebro-spinal system than aconite possesses. The action of atropia upon the respiratory centres is most marked, and is quite equal to that exercised by strychnia and ammonia. Its action is decidedly stimulating, and its potency in opium poisoning is due to its effects upon the respiration (and the circulation) when failing. That it does not exercise its influence through the vagi is proved by the fact that Bezold and Bloebaum found that acceleration of the breathing was produced by it after the vagi were cut. H. C. Wood says that it is the only known drug which exerts a decidedly stimulating effect upon the respiratory centres. He is

in error here in making this statement that it is the only agent, as the foregoing experiments and observations show. Further, he himself states elsewhere, that ammonia is an intense direct stimulant to the respiratory centres in the medulla oblongata. Certain it is that belladonna is a most potent agent in opium poisoning, "where its main influence for good is upon the respiratory centres." Prof. Frazer found atropia to at once restore the failing respiration and circulation in Calabar bean poisoning, the acceleration of the rhythm of each under its influence being very marked. The writer also noted how the failing, gasping respiration in poisoning by aconite became restored under the influence of belladonna. There can exist no longer any doubt that we possess in atropia, in strychnia, and in ammonia, most powerful means for acting upon the respiratory centres when these are being paralyzed by toxic agents.

From what has now been said it is clear that we are already in possession of agents which exercise a direct stimulating effect upon the respiratory centres; as well as agents which exercise a decided paralyzing effect upon these centres. It may now be well to consider what use may be made of such knowledge of the action of these respective drugs in the treatment of disease. We may classify these agents as (1) Respiratory Depressants, and (2) Respiratory Stimulants.

RESPIRATORY DEPRESSANTS.

To take the Respiratory Depressants first. It is clear that there are two lessons to be learnt from our acquaintance with the fact that certain agents depress the activity of the respiratory centres. The first one is a most instructive one; withal it is a purely negative lesson. It is this: Whenever the respiration is oppressed and severely taxed, as in cases of severe bronchitis, or extensive pneumonia, and still more in œdema of the lungs, sedatives are not to be exhibited. The sedatives most in use, and most likely to be selected to give relief, or procure sleep when absent in the above cases, are opium or chloral. But if these agents exercise a potent influence over the cerebro-spinal centres generally, and by arresting their activity procure sleep—and this they certainly do—we must remember that they exert a still more pronounced power over the rhythmically discharging centres which preside over the respiration and the circulation; that in fact they kill by their effects upon these very centres. The well-known empirical rule not to employ narcotics in such forms of sleeplessness is founded upon a painful experience of the dangerous and disastrous consequences of the exhibition of such agents in cases where the breathing is much oppressed and failing. How such unfortunate results should ensue becomes now plain and intelligible enough when experimental investigation has

come to the aid of empirical observation, and pointed out the special action of these two powerful narcotic agents upon the respiratory centres, and upon other centres, on whose activity in keeping up the action of the accessory muscles of respiration the very existence of the patient depends during dyspnœa. If the voluntary efforts to maintain respiration—and in dyspnœa the voluntary efforts of the individual are added to the energetic explosions of the respiratory centres—are arrested by sleep, then it becomes eminently doubtful whether the activity of the automatic centres in the medulla can carry on the respiration efficiently or not. The life of the individual depends upon the energy with which forcible respiration is maintained, and if these efforts be arrested by a narcotic, the patient then sleeps ; but it is to be feared that the sleep will be one which knows no awakening. Under the circumstances of dyspnœa, due to demonstrable organic disease, the administration of narcotics is very unsafe, and should be avoided. The danger of death from arresting the voluntary efforts is much increased by the powerful effect of these narcotic agents upon the centres in the medulla diminishing their activity, and thereby reducing the muscular efforts set up by the rythmic explosions of the automatically-acting centres.

The action upon the respiratory centre is such that it lowers the energy of this centre, and of the efferent impulses which are sent out therefrom to the muscles connected with respiration. The great danger to life

is the failure of the respiration, and this danger is much increased if drugs are given whose action is pronouncedly to paralyze those very centres which are already being overtaxed in their efforts to maintain the existence of the organism. Such is the negative lesson to be learnt about the avoidance of opium and chloral when the respiration is embarrassed.

Not only does this danger exist if opium or chloral be given during acute difficulty of breathing, but these agents exercise a sinister influence when given to procure sleep in cases of chronic pulmonary embarrassment. They will doubtless assist the natural inclination to sleep, which is usually strong, if sleep did not lead to difficulty in the breathing. They cause such drowsiness that the patient falls asleep, very frequently to be roused by a terrible attack of dyspnœa. The effect upon the nervous system generally has been to procure sleep, but the effect upon the rythmically discharging centres, and especially the respiratory centre, is to depress them also. Consequently the narcosis artificially produced is linked with attacks of dyspnœa, from failure of the respiratory centre during this medicinally induced sleep.

The other lesson to be learnt from our knowledge of the action of respiratory depressants is a positive one. It relates to the neurosal disturbances of the respiratory organs. These disorders are notably asthma, whooping-cough, hiccough, the well-known neurosal cough of

children and young girls,—a small cough like the cough of pulmonary tuberculosis, and often mistaken for it, the hysterical disturbances of sighing, sobbing, and the hurried breathing found in conditions of excitement and agitation, and finally paroxysms of sneezing. In all these neurosal disturbances the respiratory centre is involved, and the muscular movements associated with these acts must depend for their nervous origin upon efferent impulses flowing from the respiratory centres in the medulla. It is apparent enough that in the treatment of these conditions we must resort to agents which affect those centres in the medulla. But how are we to select our agents? and by what rules are we to be guided in our selection? Hitherto empirical experience, founded upon the remembrance of like or similar cases, has been the sole guide; because no general principles have been, nor without experimentation could have been, evolved. Such guidance, aided by a groping about and trying first one agent reputed to be useful in these conditions and then another, until either some agent did succeed, or the malady wore itself out and the last drug resorted to got the credit of the cure, or all measures failed, to the despair of the patient and the physician, has been the position of affairs hitherto. Now however something like principles are beginning to dawn upon us, and rules will probably before long be formulated which will guide us in our selection. Careful clinical observation must succeed experimental re-

search, and the indications furnished by the latter must be worked out carefully and watchfully at the bedside and in the out-patient rooms. Take a case of whooping-cough at present. We possess no rules to guide us as to whether we shall resort to belladonna, to chloral, to bromide of potassium, to lobelia inflata, or the gelseminum sempervirens ; or whether the child should inhale carbonic acid gas, as by being held in the fumes of a lime-kiln; or try inhalations of some secret preparation. The treatment is simply empirical, indeed experimental. But there seems every reason to believe —the writer dare not yet make a more positive statement on a limited experience—that by a careful attention to the rapidity of the respiration, its depth, its character, whether actively spasmodic, or gasping and labored, the agent may be selected which will, with fair certainty, relieve the case in point. Where there is excitement both of the respiration and the circulation —for they are so closely linked together that any marked condition of the one materially influences the other—then there are good grounds for giving bromide of potassium, chloral, or morphia, together with those anti-spasmodics, musk, camphor, etc., of which we have as yet no certain knowledge from experiment, but simply the legendary lore of a far-reaching empiricism. Where there is evident excitement in the respiratory centres these depressants may be chosen with much probability of success. On the other hand, where there

are evidences of more or less enfeeblement of the centres, and the respiration is labored and slow, or shallow and rapid, and still more if shallow and slow both, then the opposite class of agents must be preferred. Here further depression of the respiration is most undesirable and is to be studiously avoided. There are good *primâ facie* grounds for the resort to an agent which will stimulate the wearied centres, as in the case related before under the head of the Action of Strychnia (p. 66).

Such is the improvement which is being furnished to practical medicine by the results of speculative experimentation. There is a large mass of material already collected for the use and service of the clinical observer. There is already sufficient accumulated to point the way and give direction to clinical observation. The path is indeed even now shadowed out along which the practical physician must move towards a more accurate knowledge of the disturbances of the respiration and of the means of controlling them successfully. We already know how to discriminate the palpitation of muscular failure from the palpitation of nervous excitement; we know that the first requires digitalis, the latter bromide of potassium. So in a little time, with a neurosal cough we shall be able to discriminate those forms depending upon excitement in the centres in the medulla—requiring respiratory depressants, from those linked with enfeeblement of these centres—needing respiratory stimulants.

RESPIRATORY STIMULANTS.

From the foregoing sections of this essay it is clear that we possess agents which will antagonize the effects of certain other agents which paralyze the centres which govern the respiration. They save life under circumstances where without them death is certain. In addition to the presumption thus afforded by experimental research as to these said agents being stimulants to the respiratory centres, because they prevent death from being brought about by toxically induced paralysis of the respiration, there is much direct testimony furnished by other experiments, which tell explicitly that these agents are really stimulants to the respiratory centres. Reference has been made to this direct testimony above. About the fact of strychnia, belladonna, and ammonia being stimulants to the automatic respiratory centres in the medulla oblongata, there is no longer any room for doubt. The hypothesis that if these agents, especially strychnia and belladonna, will save life when threatened by failure of the respiration induced by toxic agents, they will also be of service when the respiration is failing in disease, is a fair and reasonable one to erect. Moreover it will be found that it is the fact already ascertained clinically, that these three agents are of the greatest service when the respiration is embarrassed in disease. The use of ammonia as a stimulating ex-

pectorant in bronchitis when the powers are failing is too notorious, too generally known, for any further reference to be made to it in an essay of this character. The utility of ammonia under these circumstances is a well-accepted fact with the profession at large. The usefulness of strychnia and belladonna as respiratory stimulants in the affections of the respiratory organs is comparatively unknown as yet to the profession, and this is specially true of strychnia. Dr. Thorowgood alone has pointed out the efficacy and potency of strychnia to give relief in paralytic asthma with emphysema, when the expiratory effort is deficient in power. Sidney Ringer states that strychnia is useful in the chronic catarrh of the stomach, which often occurs in chronic diseases, as bronchitis and dilated heart; but he says nothing of any direct action upon the respiration produced by the drug when so administered. And H. C. Wood but vaguely alludes to any such action in the general statement, that strychnia is useful in depressed states of spinal or other motor-centres. The writer however has for some time past used strychnia systematically for its effects upon the respiratory centres with very gratifying and satisfactory results. The forms of disease in which he has chiefly used it have been chronic bronchitis, especially when combined with more or less emphysema, and where the persistent difficulty of breathing—imperfect dyspnœa—has been found very exhausting and fatiguing

by the patient. The relief experienced was not alike in all cases, it is true: but in a large proportion it was very noticeable. In a certain proportion it was very decided, and the patients were greatly and materially relieved by its administration. In these cases, as in the one instanced under the consideration of the action of strychnia, there was great improvement in the breathing, it was less labored, and was once more conducted by the automatic centres in the medulla; and so the necessity for the painful laborious voluntary efforts was diminished, if not in some cases entirely done away with. This gives great relief to the patients; and it yet remains to be discovered whether resort to somewhat larger doses than those in common use will not afford relief in those cases where the ordinary doses have, more or less, failed to procure the desired results. In other cases, as for instance where a considerable portion of one or both lungs is practically, for all respiratory purposes, destroyed by a deposit of tubercle, strychnia will often enable the patient to breath more easily; and so not only afford relief from suffering, but do positive good by increasing the oxygenation, and by making the respiratory efforts more powerful and more complete.

Where there is a dilated right heart in chronic bronchitis with emphysema, and digitalis gives but imperfect relief, the addition of strychnia to the mixture will usually make it much more effective. The action of

digitalis upon the heart, improving its contractions, is not in itself sufficient in these cases; and the action of strychnia upon the respiration is required as well, in order to efficiently meet the needs of the sufferer. In these cases there is often a long history of difficulty of breathing, especially in winter weather. The respiration is permanently impaired by the ravages of emphysema, and the respiratory movements are limited and insufficient for proper blood aeration. The blood, more than wontedly venous, excites the discharging centres in the medulla, and more forcible respiratory efforts are made by more energetic efferent discharges. But this tends in time to embarrassment and enfeeblement of these centres, and voluntary efforts are induced to assist these automatically furnished efferent impulses. The shoulders are fixed in order that the accessory muscles of respiration may act more energetically, the gait is stiff, and the movements restricted. The powers are taxed by the respiratory efforts, and all accessories are called into play. When winter comes, and the calibre of the air-tubes is diminished by the swelling of the bronchial mucous lining, the respiration is still further impeded. It is under these circumstances that strychnia seems to exercise so beneficial an influence. The stimulation of the automatic centres thereby renders the resort to conscious effort less imperative; and so the patient is relieved, not only as regards his subjective sensations, but the

respiration becomes at once more efficient as well as easier. In these cases the right heart is almost always involved, and becomes dilated and enlarged in consequence of the impeded pulmonic circulation, and the increased obstruction to the blood-flow to be overcome. It is apt to falter too, and unless digitalis and strychnia be given together, the patient is apt to sink below the point compatible with life. Of course it is necessary to conserve the patient's powers to the utmost, to reduce the demands upon him to a minimum; and these ends are best achieved by putting him to bed. By so doing the body heat, but imperfectly furnished by impaired respiratory interchanges, is conserved; by perfect quiescence all demand upon the system is reduced to the lowest point, and the systemic forces and the nutritive processes can both be centred upon the respiratory muscles and mechanism, whose exhaustion is threatening. Sufficient nutrition to supply the requisite pabulum must be secured by the exhibition of suitable food—suitable alike in quality and quantity—small amounts given at not too distant intervals are desirable; for the wear and tear must be met by nutrient material to the nerve centres themselves, as well as to the muscles acting under their control. Having secured these different fundamental measures, then the good effects of the special agents may be put in force with a reasonable expectation of success. If they be tried in conditions which do not admit of possible suc-

cess, then of course they fail. But if the conditions under which they are tested are fairly good and favorable, then results will be attained which will leave no doubt upon the mind of the observer as to the efficacy of these respiratory stimulants.

In cases of pulmonary tuberculosis, where the lungs are more or less crippled and their structure impaired by deposits of solid material in them, the breathing is very commonly labored and uncomfortable. Here again the automatic actions are insufficient, and voluntary effort is evoked to supplement them, together with the discomfort and sense of gathering exhaustion which dyspnœa, when protracted, induces. In such cases strychnia acts not only as a useful general tonic, but as in the illustration given above, it acts specially upon the respiration, and gives relief. An extensive experience of both these classes of cases enables the writer to be pretty positive about these statements. Strychnia is, then, a tonic specially adapted to those cases of general debility where the respiration is embarrassed.

Belladonna, too, possesses similar properties, and as we have seen, is a direct stimulant to the respiratory centres in the medulla. Its efficacy in certain respiratory disorders has long been recognized empirically, and it has been largely used in certain neurosal affections of the respiratory organs. Its good effects have until recently been attributed solely to its action upon

muscles, and the leading theory of its action was that it relaxed muscular spasm. But seeing that in many cases there is no muscular spasm to relax, it seems difficult to admit this as a sufficient explanation. Further, there is a whole mass of evidence from various sources that it has a powerful action upon the respiratory centres. Meigs and Pepper are very positive about the usefulness of belladonna in whooping-cough; and the observations of Dr. Charles Kelly demonstrate that larger doses than those in ordinary use are desirable with children, who are much more tolerant of belladonna than adults are. It is stated by writers that belladonna is especially useful in the third week of the attacks when the febrile stage is over, and the convulsive attacks are diminishing in violence. As stated above, it is now necessary that the surroundings of each case of cough be carefully noted and weighed before deciding whether to resort to a sedative like chloral or bromide of potassium, or to a respiratory stimulant like atropia.

Hyde Salter found belladonna to be useful in cases of asthma where there was also oppression of breathing and cough; only he found that in order to be useful in these conditions it must be given in considerable doses. From the foregoing survey the utility of belladonna in such cases is readily intelligible, and its stimulant effect upon the respiratory centres will have excellent effects in maintaining the respiration under the difficul-

ties of spasm of the bronchial muscular fibres and diminution of the calibre of the air tubes in consequence ; just as we have seen it is of service in chronic bronchitis especially when the calibre of the air-tubes is diminished by swelling of their mucous membrane.

The relations of pulmonic respiration to cutaneous respiration and the occurrence of perspiration when the respiration is impeded, suggests the hypothesis alluded to before, that in the relief of the night sweats of phthisis the good effects are not solely due to the effect of belladonna upon the sudoriparous glands. It is well-known that these sweats are most profuse when the sleep is profound and coma-like ; and that when the patient remains awake the perspiration is less. When sleep is procured by opium or morphia the sweating is very profuse. The diminution of the respiratory movements in deep sleep, especially when artificially induced by agents which also act powerfully upon the respiratory centres, may induce compensatory cutaneous action and so supplement the pulmonic deficiency. Thus belladonna, by maintaining the respiration and preventing or antagonizing the effects of the morphia upon the respiratory centres when administered along with it may, to some extent, prevent the necessity for profuse sweats ; as well as check the action of the sudoriparous glands. The pill of one-third ($\frac{1}{3}$) of a grain of morphia with one-thirtieth ($\frac{1}{30}$) of a grain of atropine in use by me at the Victoria Park Chest Hospital for the

relief of the sleeplessness due to a racking cough in the phthisical, and which relieves the cough effectually—while the belladonna prevents the profuse perspirations which ensue when morphia in sufficient dose is given alone—is an effective one in practice. But the action of the belladonna upon the respiration must not be overlooked, or under-estimated as a possibly important factor in the production of the results.

It is not only in these more permanent conditions of disease of the respiratory organs that the agents strychnia and belladonna are of service. If space permitted, details of cases of acute bronchitis treated successfully by strychnia, when death seemed imminent, could be related.

Heat.—Before leaving this deeply interesting subject of the effects of agents upon the rhythmically discharging centres of the circulation and respiration, it will be well to consider the effects of temperature upon these centres. It is a very important subject, and one that possesses a high practical value. When a frog's heart is taken out of the body and laid upon a plate its contractions in time become deficient in vigor and much slower. If the plate be gently warmed the contractions become more frequent and more vigorous, illustrating distinctly the effects of temperature upon the cardiac ganglia. So much for the centres of the circulation: now for the effects of temperature upon the respiratory centres. "If the blood in the carotid

artery of an animal be warmed above the normal, dyspnœa is at once produced. The over-warm blood hurries on the activity of the nerve-cells of the respiratory centre, so that the normal supply of blood is insufficient for their needs" (M. Forster). Thus we see that if the blood be of a high temperature it increases the intensity of the discharge from the nerve-cells of the respiratory centres, and the energetic actions of dyspnœa are induced. The hurried and excited respiration of febrile conditions contrasts with the slow and labored respirations of conditions of low temperature. The effects of a low temperature upon nerve centres have not yet been systematically studied in warm-blooded animals ; but from observations made upon other parts of the nervous system of the frog than its cardiac ganglia, the effects of cold are to benumb nerves, it seems, while high temperatures excite action. Thus when warmth is applied to motor nerves, contractions of the connected muscles ensue ; and if the heat be greater, clonic pass into tetanic spasms. Further experiments are desirable to develop this important subject.

The subject is indeed one of great practical importance, and is not merely scientifically interesting. When the respiration is labored, or the circulation is embarrassed, the organism does not evolve heat as efficiently as it does ordinarily, and the patient is apt to become chilled. This lowering of the body-temperature causes lessened activity in the rythmically dis-

charging centres, and the tendency is for the patient to fall into a state of collapse. This statement does not rest merely upon clinical observation, but is corroborated by experimental research. Walther found that rabbits which had been artificially cooled to a low temperature (48° Fahr.) and kept in a medium not warmer than themselves, had not the power of regaining their normal temperature. But if artificial respiration were resorted to, they did recover their normal temperature: that is, by artificial means chemical interchanges were kept up, and, when a certain point had been reached, the automatically acting centres were enabled once more to carry on their functional work efficiently. The recognition of the effects of temperature upon the cardiac and respiratory centres is most important in practice, especially in cases where both the respiration and the circulation are embarrassed, as in cases of chronic bronchitis combined with emphysema. In these cases the tendency to become chill—not so much by any great heat-loss as by defective heat-production—is very marked; the patient feels cool to the hand, and the temperature is below the normal to the thermometer. In exhibiting drugs which act upon these centres this must be borne in mind in calculating the effects produced; and in patients suffering from such diseases as cripple their respiration and limit the chemical interchanges induced thereby, it is most necessary to see that their body-

heat is economized and conserved to the very utmost. Not only should they be warmly clad in flannel, or even fleecy hosiery, but they should be kept in a comparatively high temperature, up to 60° Fahr.—if higher the breathing would be embarrassed; and by means of hot drinks and warm food their body-heat should be maintained as far as possible. In addition to this, hot poultices should be kept over the chest, for by such means the cardiac ganglia may be stimulated. All are familiar with the good effects of hot poultices in cardiac embarrassment and with the relief furnished thereby, the heart recovering itself under the influence so brought to bear upon it. By such means the action of agents which stimulate the respiratory and cardiac centres may be rendered more certain and more efficient. In making systematic trial of these agents the body-temperature of the patients must be taken into consideration. It is almost impossible to procure the desired effects, at least with such doses as at present alone are thought safe to be administered, in those gelid creatures seen in our out-patients' rooms in winter. They are so placed that no fair estimate can be made of the effects of these remedial agents upon them. The temperature of all patients who suffer from extensive disease of their respiratory organs must be artificially maintained at the normal point, if the circulation and respiration are to be carried on efficiently; or be roused by the administration of agents which stimulate

the activity of these centres. The labored breathing of chronic asthmatic patients is aggravated in cold weather; and they are comparatively comfortable in bed, not only as to their ordinary sensations, but as to their respiration; and the painful efforts of dyspnœa can so be largely reduced, and relief be so afforded.

The effects of temperature are most important, and must be borne in mind carefully in all attempts to stimulate the respiration and the circulation, by means of agents which act upon the rhythmically discharging centres, which evolve the impulses that maintain the muscular movements necessary to each.

Of course, too, again comes in the purely negative lessons to avoid in such states drugs like chloral and opium, however much the appearance and the distress of the sufferer excite our compassion. To give them —at least in such doses as will give relief—is to run the risk of stopping the action of these centres altogether; indeed of killing the patient. Unfortunately but too many instances have occurred to those whose experience is extensive, to leave any doubt upon their minds as to the great danger of giving sedatives in these conditions; and that apparent hard-heartedness towards suffering is often the only safe attitude to maintain.

This subject of the effect of temperature upon the respiratory and cardiac centres has a very practical bearing upon cases where artificial respiration has to

be maintained. In spite of all efforts, respiration fails in many cases, as opium poisoning, etc. It is necessary to remember that the good effected by the artificial respiration may be more than counterbalanced by the bad effects of a falling temperature. The heat-loss may be silently counteracting all the efforts; and it is very necessary when artificial respiration is resorted to that the patient be kept warm by suitable garments, and if necessary by a high surrounding temperature.

This brings the second section of this essay to a close. The practical use of antagonism will now engage our attention.

CHAPTER VI.

PRACTICAL USE OF THE ANTAGONISM OF DRUGS IN ACTUAL POISONING.

This is a very interesting outcome of the foregoing experiments. It will be seen that the recent application of the information acquired by experimentation is opening up a field of practical knowledge hitherto scarcely entered upon. It is not only that our knowledge of the antagonism of certain toxic agents is leading to a bolder use of the different drugs in ordinary practice —because we can readily resort to an antagonist when needful, and when the indications are serious, and grave consequences are impending—but that physiological antagonists can be given when life is gravely threatened by toxic, or even lethal doses of certain poisons, taken either accidentally or by design. A few illustrative cases of such use of the knowledge of the antagonism of drugs may now be furnished.

It will be well to commence with some instances of the antagonism of belladonna and morphia, taken from the list of twenty-one cases collected by John Harley in his work on *The Old Vegetable Neurotics*. A

person took an ounce and a half of tincture of opium, and at the lapse of twelve hours was deeply comatose. Betwixt the fourteenth and seventeenth hours half an ounce of tincture of belladonna was given in divided doses; at the seventeenth hour effectual dilatation of the pupils was achieved, and the patient rapidly recovered.

In another case nine grains of muriate of morphia in solution were taken in thirty-six hours. When seen there was profound coma. The respirations were but four or five in the minute, and the breathing was stertorous. The pulse was slow and feeble. The pupils were contracted. During four and half hours after this time six drachms of tincture of belladonna were given in ʒ (drachm) doses at intervals. At the end of fourteen hours from the commencement of this treatment the coma had entirely gone. The pulse was 120; the respirations twenty to twenty-five per minute. The patient made a perfect recovery.

A very remarkable case is one recorded by Dr. S. Weir Mitchell, given in the *New York Medical Journal*, vol. iv. p. 116. The patient had taken five (5) grains of sulphate of morphia. The treatment consisted of six drachms of tincture of belladonna by the mouth and rectum, and one-third ($\frac{1}{3}$) of a grain of atropia subcutaneously at intervals. It was necessary, in addition, to resort to the galvanic current, and freely so, from the sixth to the eleventh hour, when the

action of the morphia was most apparent. The respiration was maintained at from sixteen to twenty per minute. The patient ultimately recovered.

A case of belladonna poisoning treated by opium may be contrasted with these three cases. A quarter of a grain of atropia had been administered by mistake subcutaneously. In four and a half hours there was delirium, agitation, the pulse was small and frequent, the respiration hurried and the skin hot, the face being flushed. At the fifth hour half a grain of morphia was injected under the skin; the patient became calmer, dozed, then fell asleep, and ultimately got quite well.

These cases illustrate the practical utility of our knowledge of the antagonism of belladonna and morphia, or opium.

It is unnecessary to multiply these cases by quoting any more. The antagonism of morphia and atropine, especially on the respiration, is well borne out by those cases.

Since writing the above an opportunity of treating a case of opium poisoning has occurred to the writer, and the treatment was conducted on the principles laid down in these pages; the effect on the respiration was carefully noted, and the danger of loss of body-heat from the failing respiration borne in mind.

On Feburary 14, 1878, on arriving at the West London Hospital at the usual hour, the writer was in-

formed that a woman was in the hospital at the point of death from opium poisoning. As far as could be ascertained she had taken from twelve to seventeen grains of opium, in the form of laudanum. This was at 11 A.M. She had an emetic given her at 11.30, and was then sent to the hospital. There she had another emetic administered, and the vomited matters smelt of laudanum, showing that the first emetic had not effectually emptied the stomach. Then strong coffee was given her, and she was walked about. The respiration was failing and was almost gone when the patient was seen by the writer at 2 P.M., the pulse being rhythmical and regular, though small. This showed the imminent danger to life from failure of the respiration. Being familiar with the effects of the injection of atropia on rabbits when the respiration was failing from the effects of aconitine, it was determined to administer such a dose of atropine to this patient as should have a pronounced effect upon the failing respiration. Consequently Mr. Lucas, the senior house-surgeon, was directed to throw into her subcutaneously a grain of sulphate of atropia, which he did. This was done at 2.15; for ten minutes more the respiration went on still further failing—for some time is required for the absorption of the atropine—so the patient was put into a warm bed with a bottle of hot water to her feet. By the time this was done (other ten minutes) the respiration was noticed to be

returning. There were four or five shallow respirations, with a long-drawn sigh each minute. The pupils were widely dilated. At 4.30 the woman was breathing steadily thirteen to the minute, the respiratory act being long and deep. The pulse was 132, full and compressible, while the temperature was only 97.5°, showing how it had fallen. At 8.30 the pulse was 128, the temperature 100.4°, and the respirations twenty-four per minute. She was sleeping deeply, but could be roused for a moment or so. At 1 A.M. of the 15th she was able to be roused up to talk a little, though not rationally. The respirations were now twenty-five in the minute, the pulse 120, and the temperature 100.3°. The pupils were natural. At 10 A.M. she was conscious and thirsty, but did not complain of much dryness of the throat. At 4 P.M. the pulse was ninety-six, and the respirations twenty; the temperature 101.1°, pupils slightly dilated, and the patient perfectly rational. This was twenty-nine hours after taking the laudanum and twenty-six and a quarter after the administration of the atropine. On the night of the 16th she was restless and noisy, and on the 17th was apparently suffering from *delirium tremens*, and removed to the workhouse.

It seems scarcely probable that the belladonna had anything to do with the cerebral excitement, for all its other effects had passed off some thirty hours before, and it was fifty-three hours after the injection of the atropia. It seemed more as if the patient had re-

lapsed into the condition she was in when she originally took the laudanum. As to the antagonism of these two drugs, it seemed that the effect of the atropia was far greater on the respiration, the circulation, and the temperature, than on the sensorium; for the patient slept soundly, and when aroused was not excited, while the respiration and the circulation rose.

The only mishap was a blister on each leg from the effect of the hot bottle. On the day week after her suicidal attempt she appeared before the magistrate to answer for her offence.

The dose of atropine here administered was large, but then the emergency was great. The results justified it however. It is probably the first time a lethal dose of one poison has ever been deliberately given to a human being to antagonize the toxic effects of another poison. Dr. John Harley states in a letter to the *British Medical Journal*, March 2d, that a grain of sulphate of atropia will usually prove fatal, even though another poison be previously present; but what data he has for such a statement he does not say; nor am I aware of any experiments as to the antagonism of atropia and opium that have been performed on man with grain-doses of atropia, which alone could entitle him to make such a statement.

If a case of opium poisoning were to present itself to me again, especially at an early stage, where I could carry out my ideal plan of treatment, it would go as

follows:—First empty the stomach thoroughly, then inject a fourth or a third of a grain of atropine before the respiration is gravely affected; then put the patient to bed and carefully note the respiration, the pulse, and the temperature. If the respiration was still falling half an hour after the administration of the atropine, to inject another third of a grain, and still to take careful notes; and give a third of a grain, or even more, if the respiration still fell. By such means probably it would be possible to detect any great susceptibility to belladonna in the case operated upon; for this varies greatly, as my experience at Victoria Park Hospital tells me very distinctly. With some patients it takes one twenty-fifth ($\frac{1}{25}$th) of a grain of atropia to produce the effects readily attained with one seventy-fifth ($\frac{1}{75}$th) of a grain in others, viz., arrest of the night-sweats, with some dryness of the throat and some disturbance of vision. This susceptibility to or tolerance of belladonna must ever remain a disturbing factor in the treatment of every case of opium poisoning; but the one must be borne in mind as well as the other, and the operator must see that in his fear of having a patient to deal with who is very susceptible to belladonna, and in his anxiety to avoid subsequent atropine poisoning, he does not let a life slip through his hands from the patient being one of those who is very tolerant of belladonna, and requires it exhibited freely. Such risk each man must run for himself: it

is unavoidable. If the patient were at the point of death, as in the case above, the most timid need not fear to give half a grain of atropine at once, and follow it by a second if at the end of an hour marked improvement had not set in. But such an advanced condition should never in the future be reached before atropine is used.

By giving the atropine in the manner described above, the risk of atropine intoxication will be largely avoided. Even if toxic symptoms are produced, they may become decided, especially as regards delirium, without any serious danger to life. Every case of opium poisoning for the future should be regarded as an experiment to be carefully observed; and if this be done, and the treatment skilfully applied, much information, as well, probably, as success, will be furnished thereby.

The application of the knowledge of the antagonism of remedies to the treatment of strychnia poisoning furnishes some startling results. So early as 1867 Dr. Keyworth resorted to Calabar bean in a case of strychnia poisoning. A lunatic took a packet of Battle's vermin-killer, which contained, from an estimate made of like packets, three grains of strychnine. This was at 11 P.M. At 7 A.M. next morning she was seen by Dr. Keyworth, her muscles were rigid and relaxed at intervals, and she had been in this condition since 2 A.M. He sent for some tincture of Calabar bean, and

of this he administered half a drachm every half-hour till four doses were taken; then half a drachm at the lapse of an hour, and repeated the next hour; and then fifteen minims every two hours. Half an ounce was given in all. When first seen the pulse was thin and weak, and the patient could scarcely speak or swallow. The effect of the Calabar bean in relaxing the spasms was seen in twenty (20) minutes after the administration of the first dose, and became more marked after each repetition. The case entirely recovered. This case was not treated by Calabar bean on any distinct theory of its being an antagonist to strychnia, but on account of its having been successfully used by Dr. Eben Watson of Glasgow in cases of tetanus. The antagonism of the two agents was however well demonstrated by the results.

A still more remarkable case is one recorded by Dr. Charteris of Glasgow. A butcher in Glasgow swallowed two sixpenny packets of vermin-killer with suicidal intent. He had taken the poison at 11.30 A.M. on a full stomach, which apparently retarded absorption. An emetic had been administered at 1 P.M., and at 3.30 P.M. he was carried into the Royal Infirmary, where the house surgeon used the stomach-pump. At 4.50 Dr. Charteris saw him and prescribed a drachm of the syrup of chloral hydrate, of the strength of ten grains to the drachm. In twenty minutes this was repeated, and at 5.30 P.M. two drachms were given.

After a severe spasm he was much better, but the breathing was still hurried. At 6 P.M. another drachm was given, and the spasm following this was much less violent. At 7 P.M. another drachm dose was given, and at 9.30 P.M. a final dose. Thus altogether he got ten drachms of the syrup, or one hundred (100) grains of chloral. He ultimately made a good recovery.

This case contrasts well with that recorded by Levenstein, and alluded to before, where a man aged 35 was poisoned by six drachms of hydrate of chloral. Knowing the observations of Oscar Liebreich as to the antagonism of strychnia and chloral hydrate, he determined to try the effects of strychnia. The account of this case, as given by Sidney Ringer, is as follows: "When first seen he lay in a profound sleep, with congested face, heavy breathing, and a pulse of 100. An hour after the poisoning he became livid, the veins were distended, the respirations were intermittent, and his temperature was 103° Fahr. A hour and a half after the dose he became pale, pulseless, with contracted pupils, and his temperature had sunk to 91.2° Fahr. Nitrate of strychnia, enough to produce twitching, was then injected hypodermically, and the heart began at once again to beat, and the thermometer marked 91.9° Fahr.; collapse, however, returned in a few minutes, the circulation appearing to stop. Artificial respiration was performed, and nitrate of strychnia again in-

jected, with the same result as at first. In ten hours the pupils acted to light; in twelve the temperature was 100.4°; in twenty-two hours he could be roused, and after thirty-two hours he awoke 'quite refreshed,' and did not complain of any gastric disturbance." These two cases are very important as demonstrating the antagonism of these two drugs in man as well as in animals.

Dr. H. C. Wood gives a brief allusion to a case of strychnia poisoning successfully treated by bromide of potassium. It occurred in the hands of Dr. Cephas L. Bard, who reported it in the *Philadelphia Medical Times*, vol. i. Three grains of the alkaloid had been taken, and there was no vomiting; but under the exhibition of half an ounce of bromide of potassium, followed up by smaller doses for an hour or so, the patient recovered. The symptoms were as intense as were compatible with life; but general relaxation was produced in thirty minutes after the ingestion of the counter-poison.

Another highly instructive and interesting case of the use of the antagonism of drugs in actual poisoning is related by Dr. William Dobie, of Keighley, Yorkshire. It goes as follows: "A veterinary surgeon determined to commit suicide, drank freely, and then took a quantity of aconite; how much is not certain. Dr. Dobie saw him in a few minutes, and administered an emetic. At this time there were no symptoms of

aconite poisoning. Half an hour later he returned with his partner, and found that the emetic had acted, and that the bowels also had moved. At this time the pulse was rapid and feeble, and the hands and feet were getting cold. "An attempt to give ammonia and brandy brought on alarming prostration; the breathing became labored; the pulse at the wrist irregular, intermittent, and finely imperceptible. There was a quantity of frothy mucus discharged from the mouth and nostrils; the skin became dusky; a cold clammy sweat bedewed the face and forehead; in a word, the patient was dying." So runs the report: and the vivid sketch shows how close a similarity there exists in aconite poisoning betwixt the symptoms in man and those exhibited by animals. As the patient was unable to swallow, twenty drops of tincture of digitalis were injected subcutaneously, and galvanism applied to the cardiac region, and kept up for twenty minutes. A minute or two after this the patient was able to swallow some ammonia and brandy, with a teaspoonful of tincture of digitalis in it. Marked improvement followed, and this mixture was twice repeated within an hour, "by which time the breathing had become easier and the circulation re-established." The patient recovered perfectly, and next morning expressed his surprise at being alive, as he had taken, he asserted, an ounce of Fleming's tincture of aconite. The early administration of

the emetic no doubt prevented the absorption of a large quantity of the poison, but enough had been absorbed to produce the most serious symptoms. The small quantity of aconite left in the bottle was tested, and it was found that two minims killed a young sparrow in $3\frac{1}{2}$ minutes, while the same quantity of a fresh specimen was thirty seconds longer in producing a fatal result. It is impossible to avoid the conclusion arrived at by Dr. Dobie, that the digitalis was the great factor in the production of the favorable result, though no doubt the ammonia helped. Dr. Dobie states that the idea of using digitalis in this case was suggested to him by his acquaintance with my experiments, performed for my Essay on Digitalis.

These cases furnish the final corroboration requisite to demonstrate the antagonism of drugs within the organism, and to show how research upon animals can be utilized for the needs of human beings. They illustrate that the action of drugs upon animals is sufficiently near their action upon man to furnish guidance for their use practically in cases of poisoning. Slight modifications in their general actions there may be, true; and the results of experimentation upon animals cannot be applied absolutely to man. But how nearly they come the foregoing cases show. Enough has already been achieved to place beyond all doubt or cavil the fact that certain toxic agents antagonize each other within the system; and that a lethal dose of one

poison will be survived if a sufficient dose of another toxic agent be given in sufficient time. What these different antagonistic agents are, in the present state of our knowledge, and how they act, has been related in the past pages of this Essay.

The last thing that remains to be done is to review the subject of the practical value of such acquaintance with the antagonism of remedial agents, and how far such knowledge can be made serviceable in the ordinary routine of practice.

CHAPTER VII.

USE OF ANTAGONISM OF DRUGS IN ORDINARY PRACTICE.

The lessons taught by the foregoing examination of the antagonistic action of certain toxic agents may be summed up as follows.

Circulation.—We possess in digitalis, in belladonna, in casca, and strychnia, agents which distinctly act upon the heart, and produce more perfect ventricular contraction when it becomes necessary or desirable to excite this, as in conditions of cardiac debility either temporary or permanent. In toxic doses, such as are not in any way serviceable in practice, these drugs arrest cardiac action: but in medicinal doses they are perfectly safe and trustworthy.

On the other hand, in aconite, in veratria, in chloral, in morphia, and in Calabar bean we possess cardiac depressants of a potent character, which may be used with advantage where there is vascular excitement and the heart's action is powerful and it becomes desirable to lower or moderate it. But these depressants are liable at times, from causes not always appa-

rent, to produce much more depression than is sought, and so to threaten life. They must be used cautiously and watchfully. They are contra-indicated in all conditions of cardiac asthenia or embarrassment.

One class of agents excite action in the rhythmically-exploding cardiac ganglia. The other class lower the activity of these rhythmic centres.

Respiration.—In like manner are the agents affecting the respiration to be arranged. We have seen that there are agents which stimulate and those which depress the respiratory centres in the medulla oblongata. The first class comprises the true stimulant expectorants, viz., ammonia, belladonna, strychnia, and some other agents—as senega, ammoniacum, and squill, whose actions have not yet been carefully examined into. Squill acts powerfully upon the heart. Several observations have been made as to this action, and it has been found that squill excites increased ventricular contraction, and that, too, markedly. There seems every reason to believe, in the absence of any direct information, that squill acts, too, on the respiratory centres, and is, like belladonna, a direct stimulant of these centres.

These stimulant expectorants can be used with advantage when the respiration is embarrassed. They enable the patient to breathe more perfectly, and so give relief in conditions of oppressed respiration.

Consequently we see that expectorants must be

divided into two classes: (1) the true stimulant expectorants, and (2) those which act upon the bronchial lining membrane and increase the secretion of phlegm.

The first enable the patient to breathe, and so to cough more efficiently; the second make the mucus less tenacious, so that it is more easily coughed up. Ammonia represents the first class, and iodide of potassium the second. Thus in a case of severe bronchitis, where the respiration is embarrassed and the secretion not very loose, these drugs would be combined and given in a vehicle like senega. In a case of chronic bronchitis strychnia or belladonna would be added to an alkali and to an agent like ammoniacum. So too strychnia or belladonna may be administered in acute affections where the respiration is falling. Thus in a case of acute bronchitis where the phlegm is loose, the patient bathed in perspiration, and the powers failing, ammonia and strychnia should be given together in a vehicle like squill, senega, or ammoniacum. In chronic conditions the same form of combination may be resorted to with advantage.

A few cases illustrating the utility of strychnia and belladonna as stimulants to the respiratory centre may now be advantageously recorded. The first is an acute case, where the effects were most satisfactory. It is furnished me by my friend Dr. D. Thomas, of Ystalyfera, and occurred in October, 1873. "W. R.,

æt. 48, working in a tin-plate factory, of fair healthy constitution, though not very robust, was seized with well-marked rigors, headache, and vomiting. Very early the respiration became hurried and very disturbed, with a temperature at times 103°. The symptoms throughout were of an aggravated character, and towards the eighth day much exhaustion and weakness were present. The treatment at first was of the ordinary kind. But as soon as the adynamic symptoms came on we gave all the stimulants and the most supporting diet we could think of. Notwithstanding all this, towards the eighth day he seemed to be getting more and more oppressed in his breathing, with, as I have in my notes, 'the weak, irregular pulse of a dying man.' In this stage I gave him tincture of digitalis, tincture of nux vomica, and carbonate of ammonia. Next day my report was, 'W. R. wonderfully better. I would not believe any drug could have such an effect upon the pulse as digitalis must have had upon his.' He made a capital recovery, and has enjoyed admirable health ever since." Here, doubtless, the effects of the ammonia and strychnia upon the respiratory centre, as well as those of the digitalis upon the cardiac ganglia, must be taken into the calculation as to the satisfactory results obtained.

My colleague, Dr. Thorowgood, has told me of a case of desperate bronchitis, where the addition of

strychnine to the mixture made all the difference apparently betwixt life and death; but, unfortunately, he has kept no notes of the case.

No opportunity of treating acute bronchial affections has offered itself to me since the formulation of the above views about belladonna and strychnia; but an extensive experience of them in chronic conditions has satisfied me as to their usefulness in practice. Of course, all cases are not markedly benefited by the use of these agents; but the great majority decidedly are benefited thereby. The following are a few of the most complex cases which have been successfully treated. In each, in addition to the disease, there was also a habit of taking narcotics. A gentleman came under my care last October in the following condition. He had œdema in both legs, his heart was that of a gouty man, and the hypertrophy was failing, and there was some irregularity in his pulse. He was a gouty man, and some joints were crippled by gout. His chief complaint was difficulty of breathing, aggravated by flatulence. The breathing was persistently difficult, and in the night he was subject to distressing attacks of dyspnœa (uræmic dyspnœa), which tried him sorely. He also had much itching of the skin. He had acquired a few years ago the habit of taking some Battley's sedative for a very painful affection, and continued it, apparently not being able to abandon it without suffering. He always had some at bed-time,

as without it he could not sleep. Seeing that it was clearly undesirable to stop the opiate, I put him upon strychnia. In a fortnight the attacks of dyspnœa had entirely disappeared, the pulse was improved, and the œdema was reduced. The flatulence was much better, but still troublesome. The improvement steadily continued, until a thick fog in January set up inflammation of the bases of both lungs. The breathing was much embarrassed, as might be expected, but through it all there was never an approach to an attack of dyspnœa. His family and nurse often remarked this, saying that if one of his old attacks had come on in the midst of the embarrassed breathing, he must have died then and there. So much tone, however, had a three months' course of strychnia given to the respiratory centre, that it never failed under the trial to which it was subjected. The œdema of the legs became great as the breathing improved: and Sir William Jenner recommended the addition of some digitalis to the strychnia pill. The œdema fell steadily; and the general condition improved under the combination; and the case is progressing as steadily and satisfactorily as such a case possibly can; the patient often stating that he feels much better than he ever expected again to feel. Here the strychnia not only improved the respiration, but warded off the attacks of dyspnœa produced by the effect of the opiate upon the respiratory centre.

In another case, a patient at Victoria Park Hospital, where there is chronic bronchitis with emphysema, equally satisfactory results have been attained. The patient, a very intelligent man, had long taken narcotics to induce sleep, under a physician as a private patient. He could not sleep without a narcotic, and then woke up constantly with an attack of dyspnœa during the night. I explained to him that, in my opinion, the attack of dyspnœa was due to the effect of the narcotic, and prescribed for him ammonia, nux vomica, and digitalis. After the first night he had no more dyspnœa, and could lie down and sleep like other people, without feeling the need of a narcotic. His gratitude has only been equalled by his surprise. The proof that this was no mere coincidence is furnished by the fact that, feeling well, he neglected to get a new letter, and was without his medicine for some days. On the third night he had an attack of his old dyspnœa, which made him return to his medicine without further delay.

A third case is furnished by a gentleman of literary habits, well read in medical literature. He was the subject of lithiasis, had corded arteries, an hypertrophied heart, with irregular action, chronic bronchitis blended with emphysema, and great vesical irritability. In addition to this there was a regurgitant mitral murmur, and he habitually took chloral at bed-time, and almost every night had an attack of dyspnœa.

This was a very difficult case to treat, through the complexities, and what "line of cleavage" was to be adopted was not an easy thing to see. His nose, cheeks, and hands were of a blue hue, from the paralysis of his peripheral arterioles by the chloral. I commenced by giving him some ammonia, nux vomica, and digitalis. He improved very considerably, and all but lost his attacks of nocturnal dyspnœa. But the strychnia so excited his irritable bladder centres, that it had to be stopped, and belladonna, which exercises the same influence over the respiratory centres, but which lessens the activity of the bladder centres, was given in its stead. This change met the emergencies of the case admirably, and the improvement was steady and gratifying. The chloral at night was not stopped, but the dose was lessened and some opium substituted. The blue hue of the face and hands has almost entirely disappeared; and what is more, the mitral murmur has vanished, and the heart beats steadily. Altogether he is very much satisfied with his progress.

These cases illustrate the potency of strychnia and belladonna, not only in diseased conditions, but also where a toxic agent is in action. The substitution of one series of agents for another series with advantage, is well demonstrated in the second case quoted. In the first case, the power of strychnia to counteract the effects of opium on the respiratory centre is well

shown. In the third case, the toxic effects of chloral was antagonized by the agents given. In this case, too, the effect of strychnia upon the bladder centres is well seen. This constitutes an objection to the use of strychnia in some elderly persons; but in these cases belladonna meets the difficulty very satisfactorily; and where great vesical irritability is complained of in cases of chronic bronchitis linked with emphysema, and found along with lithiasis, it is well to add belladonna to the mixture given, as it usually gives great relief, and thus the patients rest better at night, being less disturbed.

A number of uncomplicated cases might be quoted if it were desirable to do so. These three cases are illustrative, because in them there was not only a morbid condition, but also the effects of depressants of the respiratory centre to be combated. As well as these two classes of agents, there are the depressants, which again may be simple neurosal depressants, like aconite, Calabar bean, or chloral; or really nauseant expectorants, like tartar emetic, lobelia, and ipecacuanha, which depress the circulation (and probably the respiration as well), and at the same time cause the bronchial secretion to become freer. They are useful in the early stages of bronchitis, for instance, where the lining membrane of the air-tubes is swollen and the secretion almost wanting. This stage over, and free secretion established, then the stimulant

expectorants come in and maintain the flagging respiration, and often enable a case where the result is very doubtful to turn the corner successfully. Probably, in these cases, full doses of strychnia or belladonna are indicated in addition to the ordinary drugs employed.

In the neurosal affections of the respiratory organs, the various factors of each case must be weighed and calculated for before the choice is determined, whether a respiratory stimulant or depressant shall be selected. Where the respiration is embarrassed, a respiratory stimulant is indicated; where it is excited, a respiratory depressant will rather be calculated to be of service.

There are other uses to which these stimulants of the respiration and circulation may be put. And it will be seen that already these views have passed the merely speculative stage. In death by chloroform either the respiration or the circulation fails. Is it possible to obviate this danger by the use of some agent which stimulates the centres connected with these systems, given synchronously? It is clear that it would often relieve anxiety, to say the least of it, and be of actual service where failure of these systems may be apprehended, if such agents could be administered. Where such failure seems threatened the administration of strychnia or belladonna before the chloroform might prevent a fatal result, and in other

cases ward off serious symptoms. This is a line of inquiry well worth pursuit, and if worked out will probably give some valuable information. For even now we possess some positive knowledge about this matter. In the *London Medical Record* for July, 1877, is a brief account of some remarkable words which fell from Dr. Gaillard, before the Kentucky Medical Association. "By the occasional use of ammonia on the towel the heart can be sustained in effective action during the longest operation." The report is by J. T. Clover, whose reputation in the matter of anæsthetics is a guarantee that this idea is a good one, else he would not have recorded it in the pages of that journal. Ammonia sustains the action of the respiratory centres as well as the heart. Dr. Gaillard's idea may be found ere long to have blossomed and borne fruit of a most valuable character. The possibility of getting rid of a dangerous and unsought action of one drug by the co-administration of another must now be entertained; and all that is apparently wanted is further observation in this direction.

Such tactics need not be confined to the risks of chloroform only; they may be extended to other agents. Thus there is the pill alluded to before, where morphia and atropine are combined, so as to arrest the perspirations which would result from the exhibition of morphia alone, in doses large enough to be effective

in the sleeplessness of phthisis, where there is a racking cough. Indeed the way seems clear in the future to the administration of much larger doses of opium and morphia than are at present thought safe, if the depressant effects upon the respiration and circulation be warded off by the co-administration of atropine, which acts very specially upon these two centres. The morphia would thus act upon the other cerebro-spinal centres, and yet its effects upon these automatically-acting rhythmic centres would be largely antagonized. Thus in conditions of severe osteoid pain, or in carcinoma, in renal colic, etc., doses of opium might so be administered with safety — which otherwise would be unsafe from the unsought action they would exert upon the respiration and circulation.

This again is not a mere speculative hypothesis. A case is given in the *Practitioner* for one of the later months of 1875, where Dr. Broadbent was called in consultation by me to a case of carbuncle of the lip, and where there were delirium and insomnia, combined with great asthenia and feebleness of the circulation. It was dangerous to push opium freely alone; so it was decided to administer some digitalis at the same time to sustain the action of the heart. By this means 100 minims of tinctura opii were administered safely; the patient slept soundly, without the circulation failing, and ultimately made an excellent recovery.

A great future lies before therapeutics, apparently at least; and this power to antagonize an undesirable and unsought action of a potent remedy will add materially to its utility, and the safety with which it may be wielded in practice.

This practical use of the knowledge of the antagonism of agents, so that they may be co-administered with advantage in certain cases, is spreading rapidly. Already in our text-books are to be found directions in the treatment of atonic gout to prevent the depressant action of potash upon the heart by the co-administration of strychnia or digitalis. Some persons are readily depressed by ordinary doses of potash, and here these agents may be added to the potash mixture with advantage. In cases, too, of gout with a dilated heart potash may be given freely, even with the depressant colchicum, if digitalis be added; digitalis in no way interfering with the other actions of these agents which make them of service in gout. In like manner in atonic gout, if the alkaline treatment is found to attenuate the blood too much, chalybeates may be added to the potash mixture, and the normal condition of the blood be maintained.

In another direction the practical utility of antagonism is famously illustrated, and that is in the power possessed by hydrobromic acid to control cinchonism, and to enable quinine to be taken without discomfort

by many who without this adjunct cannot tolerate this anti-periodic.

Finally, the destructive hæmolytic action of mercury in cases of constitutional syphilis, where it must be given for long in large doses, and the cachectic condition of the patient apparently forbids its use, the co-administration of iron will be found to counteract the hæmolytic action, and permit the drug to be pushed with advantage for practically unlimited periods.

Such are the practical fruits already at hand of the growing knowledge of the antagonism of drugs. Research into such antagonism is not merely of interest to scientific men; it promises to exercise a most potent influence over, and to be of the utmost service in, ordinary every-day practice.

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